Controlled Release of an Anti-Inflammatory Drug Using Conducting Polymer Nanotubes for Neural Prosthetic Applications

Mohammad Reza Abidian[1] and David C. Martin[1, 2, 3]

[1]Department of Biomedical Engineering, the University of Michigan, Ann Arbor, MI
[2]Materials Science and Engineering, the University of Michigan, Ann Arbor, MI
[3]Macromolecular Science and Engineering, the University of Michigan, Ann Arbor, MI

Topic area: Materials and Devices

The interface between microfabricated neural microelectrodes and neural tissue plays a significant role in the long-term performance of these devices. It is thought that biocompatible polymer coatings can stabilize the interface between microelectrode and living tissue at the site of implantation. The ability of neural electrodes to record high signals over extended periods of time remains a significant problem. The engineering of bioactive electrode coatings has been investigated for its potential to promote in-growth of neural tissue, reduce shear stress, and enhance signal transport from electrons to ions at the electrode-host interface.

We have developed a new approach for preparing anti-inflammatory, drug-loaded conducting polymer nanofibers. The fabrication process includes the electrospinning of a biodegradable polymer (here, poly(lactide-co-glycolide) or PLGA) into which a drug has been incorporated (here, the anti-inflammatory agent, dexamethasone), followed by electrochemical deposition of a conducting polymer (here, poly(3,4-ethylenedioxythiophene) or PEDOT). The conducting polymer nanotubes significantly decrease the impedance and increase the charge capacity of recording electrode sites on microfabricated neural probes. The drugs can be released from the nanotubes in a desired fashion by electrical stimulation of the nanotubes, presumably due to a local dilation of the tube that facilitates transport.

The impedance spectroscopy revealed that the impedance of gold electrode sites significantly decreased from 800 kΩ to 8 kΩ after PEDOT deposition on the electrode sites and around the PLGA fibers. The charge-transfer capacity of the electrode site increased from 0.14 μC to 1.64 μC by growing PEDOT around the PLLA/PLGA nanofibers. This value was increased significantly to 3.01 μC after making the PEDOT nanotubes. By using external electrical stimulation of the nanotubes, we can precisely release drugs at desired points in time. After the electrical excitation, we observed a significant increase in the amount of dexamethasone released. The surface morphology of the coated electrodes was assessed by optical microscopy and scanning-electron microscopy. Scanning-electron microscopy and focused ion beam showed the nanotubular structure of conducting polymers on the electrode sites.

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High Speed Optical Transcutaneous Telemetry Link

D. Michael Ackermann, Brian Smith, Kevin L. Kilgore and P. Hunter Peckham
Department of Biomedical Engineering and Cleveland FES Center
Case Western Reserve University

Local cortical field potentials can be recorded using arrays of microelectrodes placed in the cortex. These potentials are a prospective control source for neural prosthetic systems such as the Networked Neural Prosthesis System, NNPS. The current state of implanted processing capabilities and the evolving nature of control algorithms requires the processing of these cortical potentials into control signals external to the implanted device. Therefore these signals must first be transmitted to an external signal processor. Some cortical control algorithms utilize neural waveform data and spike-sorting to generate control signals (Lewicki 1998). Transmission of this continuous waveform data from multiple channels of a microelectrode array may require a transcutaneous data-link capable of 40 Mbps or greater.

High speed transcutaneous data transmission can be achieved using percutaneous wires, acoustic energy or electromagnetic energy (inductive coils, rf radio link, optical). Current systems that output continuous waveform data for all channels use a percutaneous wired connection (Cyberkinetics, Inc.). While percutaneous wires have been shown to have low rates of infection and failure and may provide an adequate data-transfer solution for short-term implantations (Knutson, Naples et al. 2002), they are considered not to be a long-term solution for transcutaneous data transfer. Cosmesis and patient acceptance drive the need for a data channel that does not physically penetrate the skin.

Of the possible wireless solutions, optical transmission appears to be the most practical implementation due to the very high data rates needed and the difficulties with physical implementation and bandwidth restrictions associated with other methods. We are developing a device capable of meeting or exceeding the 40 Mbps data rates required while achieving reasonable power consumption, robust operation and maintaining an appropriate form factor. A low data rate proof-of-concept device operating in the NIR optical band has been constructed and has been shown to be operational through several millimeters of skin.

Knutson, J., G. Naples, et al. (2002). "Electrode fracture rates and occurrences of infection and granuloma associated with percutaneous intramuscular electrodes in upper-limb functional electrical stimulation applications." Journal of Rehabilitation Research and Development **39**(6): 671-683.

Lewicki, M. (1998). "A review of methods for spike sorting: the detection and classification of neural action potentials." Network: Comput. Neural Syst. **9**(4): R53-R78.

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Wavelet-Neural Network Approach for Analysis of Visual Evoked Potentials

Jeff Anderson[1], Hojjat Adeli[2], and John Broussard[3]

[1]Ph.D. student, Biophysics Interdisciplinary Graduate Program, Ohio State University, Columbus, OH
[2]Professor, Departments of Biomedical Engineering and Neuroscience, Ohio State University, Columbus, OH
[3]Ph.D. student, Department of Psychobiology, Ohio State University, Columbus, OH

The standard method of analysis of evoked potentials has been to average the evoked potentials over many trials. This has been a useful tool in clinical diagnosis and research for many years. However, this does not allow for insight into the physiology at any given time, since sufficient time is needed to obtain the trials necessary for a good average. A wavelet-neural network method is presented for analysis of a representative visual evoked potential (VEP) to gain insight into the physiology of a recorded brain region. The goal is to determine the event of signal detection by analysis of a single VEP recorded from a rat's posterior parietal cortex (PPC) while performing a visual task. Signal detection is observed by the rat performing the visual task correctly.

The methodology consists of three stages. First, wavelet analysis was used to find key features in the visual evoked potentials that can be used to classify them in two different classifications, either as coming from a PPC that will correctly process the information (signal detection) or from a PPC that will not and, consequently, prevent the rat from performing the task correctly.

Next, K-means cluster analysis was employed to classify a large set of trials of VEP into a few clusters. These clusters represent the underlying patterns in the VEP. Finally, a radial basis functional neural network (RBFNN) was developed to determine how the clusters correlate to either signal detection or non-signal detection. The RBFNN was created using 172 VEPs and tested on 76 additional VEPs. The model can detect the correct signal with an accuracy of about 76%. This is significant, considering the fact that the rat can detect the signal correctly only about 80% of the time.

Impact of Muscle Spasms on Standing Balance of SCI subjects — A Computer Simulation Study

Musa L. Audu, Ronald J. Triolo, and Robert F. Kirsch

Department of Biomedical Engineering and Orthopedics,
Case Western Reserve University, Cleveland, OH, and
VA Functional Electrical Stimulation Center of Excellence, Cleveland, OH

A 3D bipedal model of the human musculoskeletal system was developed and used to carry out simulation studies on stability of a human standing in the presence of a wide variety of external and internal disturbances. The model is characterized by 15 degrees of freedom, mostly at the lower extremities; the segments are represented by rigid bodies; and it can be actuated by 56 muscle groups. The model exhibits a high degree of instability, typical of the actual human system, because of the inverted nature of the system with respect to the ground support.

Using the method of eigenstructure assignment, decoupling controllers were designed to control the independent joints of the model based on changes in the joint angles and joint angular velocities from a desired equilibrium posture. The controllers apply appropriate joint moments so as to restore the posture of the body from any given initial posture to the desired posture. In addition, the controllers restore the posture of the body to its equilibrium posture whenever the body is subjected to external disturbances. The model also allows for the stimulation of any muscles to simulate the effect of spasms. The muscles could be stimulated in synergistic groups or as groups of synergists at any desired point in time during the simulation.

The results of some of the simulations indicate that the standing human is most susceptible to ankle plantarflexor spasms. Whenever the soleus and gastrocnemius muscles are stimulated together at more than 40% of their maximum capabilities, the controller was unable to maintain the equilibrium of the posture. On the other hand, the results show that knee extensor spasms had the least impact on the stability of the system, although when the knee extensors were stimulated beyond 70% of their maximum capacities, the controller effort indicates that knee flexors will need to be recruited to prevent injury to the passive structures (ligaments and other tissue) at the knee.

The results of the simulations have been useful in making decisions on the best set of muscles to include in the 16-channel FES stimulating system being designed in our laboratory. The implications and limitations of the muscle set selected can be extensively studied in simulation before the system is actually implanted. Also, the results of the simulations are useful in the design of sophisticated controllers for achieving hands-free standing balance of SCI subjects with FES.

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Initiated Chemical Vapor Deposition (iCVD) of Insulating Coatings for Neural Prostheses

Neeta P. Bansal, Karen K. Gleason, and Hilton G. Pryce Lewis

GVD Corporation, Cambridge, MA

The miniaturization of neuroprosthetic technology has led to an urgent need for thin (10 μm or less) insulating coatings that retain their biocompatibility and stability over long periods. Lead wires are usually of small diameter, and are frequently insulated with fluoropolymer sleeves such as TEFLON. These provide reliable insulation, but limit the minimum dimension of wire that can be used, as well as the flexibility of the lead wire. Initiated chemical vapor deposition (iCVD) is an alternative to solvent-based techniques or powder-spraying methods for forming polymeric coatings. By avoiding solvents, the effects of surface tension and nonuniform wetting are eliminated, making vapor deposition especially useful for encapsulating objects having features or dimension of less than 100 microns, such as the fine lead wires employed to route electrical signals in many types of neural prosthetic devices. In addition, the iCVD films contain no residual solvent. The iCVD process can be performed in a single step without the need for subsequent curing treatments. For the coating process, the precursor gas, hexafluoropropylene oxide, is decomposed within a vacuum chamber held at modest pressure (~1 torr), and the object to be coated remains at ambient temperature during processing.

Under a Phase I SBIR, iterative experiments were used to identify iCVD process conditions that successfully provided electrical insulation to 25-m diameter gold lead wires. The thinness of the coating also renders the coating flexible. The coating was tested after physical stressing and exposure to a simulated biological environment and the insulating abilities were proven in short-term testing. No visible cracks or defects were observed in optical or electron micrographs after the flex testing. These iCVD PTFE coatings were demonstrated to have bulk surface resistivity greater than 10 times higher than the reported value for the commercially available insulating coating, Parylene-C. Testing by a certified outside laboratory, NAMSA, has demonstrated that our coatings meet the requirements for a USP Class VI plastic. Additionally, the chemical structure of the iCVD PTFE coating was verified to be spectroscopically indistinguishable from that of Teflon and Gore-Tex, but the precision of the gas-phase assembly process produces coating thicknesses down in the 40-nm to 10-m range. The thinness of the coatings translates into smaller and less obtrusive devices, which is critical in applications such as neural surgery and implantation. With applications for which a maximum allowable profile is specified, a thinner coating leaves a larger cross-sectional area for the active device. In the case of coated wire, increasing the cross-section of metal would increase stiffness and increase the maximum current that could be carried.

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Mechanisms of Electric Field Effects on Network Excitability in Hippocampal CA1

Julia Berzhanskaya[1], Nick Chernyy[2], Bruce J. Gluckman[1,2], and Steven J. Schiff[1,3]

[1]Krasnow Institute for Advanced Study, George Mason University, Fairfax, VA
[2]Department of Physics and Astronomy, George Mason University, Fairfax, VA
[3]Department of Psychology, George Mason University, Fairfax, VA

Low frequency (<100 Hz), low amplitude (<100 mV/mm) electric fields have been adaptively applied to suppress epileptiform activity. Such subthreshold fields modulate neuronal threshold and provide an attractive alternative to high-intensity pulsed stimulation. Nevertheless, the mechanism of interaction of subthreshold fields with principal cells and interneurons remains unknown. Here we explore mechanisms of field modulation on hippocampal network activity by recording from visually identified neurons within area CA1 of transverse hippocampal slices using whole cell recordings. Electric fields were applied through a voltage-controlled circuit in a custom-designed perfusion chamber. Afferent stimulation was used to generate EPSPs and IPSPs, and the morphology of the impaled cells was determined with biocytin histochemistry. The effect of the field depended on the neuron type and morphology. Pyramidal cells were consistently depolarized by a negative electric field aligned with the somato-dendritic axis, and hyperpolarized by a positive electric field. Interneurons showed a diverse response to weak electric fields, within a range of no effect to the same sign, and often smaller amplitude effects as compared to the pyramidal cells. The effect of the field on evoked EPSPs varied from cell to cell and was determined by a combination of changes in the transmembrane driving force for synaptic channels and voltage-gated membrane conductances as determined by dendritic tree morphology. Negative electric fields also decreased spike latency and increased the number of spikes. Effects of electric fields on membrane potential and spontaneous activity had a composite time course consisting of medium (tens of milliseconds) and slow (few seconds) phases. A complex interplay between the polarization effects on interneurons and pyramidal cells determines the effect of electric fields on network excitability.

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Bio-Heat Transfer Model of Deep Brain Stimulation-Induced Temperature Changes

Marom Bikson, Qingjun Kong, Maged Elwassif, and Maribel Vazquez

Department of Biomedical Engineering, City College of New York, New York, NY

The mechanisms responsible for the therapeutic action of deep brain stimulation (DBS) remain unclear. Fundamental questions remain about methods for optimizing stimulation efficacy and safety. It is well established that electrical stimulation of brain tissue can induce temperature rises through Joule heating. Here we investigated the magnitude and spatial distribution of DBS-induced temperature changes.

We modeled temperature changes around Medtronic 3387 leads during typical (3.0 V, 185 Hz, 90 μs activating PW) and high (10 V, 185 Hz, 210 μs activating PW) bipolar stimulation settings. The upper limits of temperature rises for a homogeneous nonperfused brain tissue were 37.05°C for typical and 38°C for high stimulation settings. These peak temperature rises were observed at the electrode surface after ~5 minutes; heat propagated into the tissue, reaching a steady state after ~30 minutes.

Increasing stimulation intensity increased the peak temperature attained, but did not affect the relative temperature spatial profile. The latter was quantified with a temperature decay constant defined at the distance from the electrode where the temperature has decayed to 33% of its peak value. Increasing the electrical conductivity of the volume increased the peak temperature rise, while increasing the thermal conductivity decreased the peak temperature rise. Neither perturbation had any effect on the temperature decay space constant. Increasing blood perfusion decreased the peak temperature rise and reduced the temperature space constant.

DBS-induced changes in brain temperature will directly modulate neuronal function as well as affect neuronal responses to ‘direct’ electrical stimulation; for example, action potential threshold, depolarization block threshold, neurotransmitter release and clearance kinetics, and peak action potential firing rate.

Computational and Experimental Responses to Paired-Pulse Thalamic Stimulation

Merrill J. Birdno[1], Scott E. Cooper[2], Ali R. Rezai[3], and Warren M. Grill[1]

[1]Department of Biomedical Engineering, Duke University, Durham, NC
[2]Department of Neurology, Cleveland Clinic Foundation, Cleveland, OH
[3]Department of Neurosurgery, Cleveland Clinic Foundation, Cleveland, OH

Previous experiments have examined the dependency of tremor on deep brain stimulation (DBS) parameters in persons with essential tremor (ET). These studies demonstrated a complex dependency of tremor on interpulse interval (IPI) during paired-pulse thalamic stimulation in ET patients. Here, we attempt to explain the dependency of tremor on IPI using a computational model of paired-pulse stimulation in populations of thalamocortical (TC) relay cells.

We stimulated eight thalami in six persons with ET through externalized DBS leads with paired-pulse trains, and quantified tremor amplitude as a function of IPI. Pulse pairs were delivered at a rate of 60-70 Hz, with IPIs ranging from 0 to 7.5 ms. Tremor suppression with IPIs less than 1 ms was less than with IPIs greater than 5 ms, suggesting that the stimulated neurons have an absolute refractory period of less than 1 ms. Further, in five thalami, tremor increased as the IPI increased from 1 ms to 3 ms, while IPIs greater than 3 ms produced tremor suppression.

We simulated paired-pulse DBS in a population of 100 independent TC relay cells distributed uniformly in a 3D sphere (radius = 3 mm). We delivered paired-pulse trains at a rate of 70 Hz and varied the IPI from 0 to 7.0 ms. We quantified the TC cell response by calculating the distribution of the interspike intervals from the responding TC cells.

At IPIs less than 1 ms, the number of neurons activated by the first pulse that were also activated by the second pulse decreased as a result of refractoriness, but the total number of neurons excited by either pulse increased, presumably due to temporal summation. Further, at intermediate IPIs (2-4 ms), the temporal irregularity of neural spiking was increased, with increased dispersion in the interspike interval histograms, while at long IPIs, neurons responded with single spikes to each stimulus in the pair. Our simulation results demonstrated a qualitative correlation between the distribution of model TC cell interspike intervals as a function of IPI, and tremor suppression in persons with ET as a function of IPI.

The complex patterns revealed in these studies suggest that both the rate and pattern of DBS pulse trains influence the neuronal response and efficacy of tremor suppression.

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Vascular Contribution to Reactive Responses Following Neuroprosthetic Device Insertion

C.S. Bjornsson[1], S.J. Oh[2], Y. Al-Kofahi[3], Y.J. Lim[3], K.L. Smith[1], J.N. Turner[1], S. De[3], S.J. Kim[2], B. Roysam[3], and W. Shain[1]

[1]Wadsworth Center, New York State Department of Health, Albany, NY
[2]Seoul National University, Seoul, Korea
[3]Rensselaer Polytechnic Institute, Troy, NY

The potential benefits of neuroprosthetic devices are limited by biological reactive responses that interfere with the brain-device interface. Reactive responses begin immediately upon insertion; however, the contributions of insertion parameters (e.g., device geometry and insertion speed) to damage are not known. We have developed an *ex vivo* system that permits collection of real-time video images of tissue deformation during device insertion, by labeling the vasculature within live coronal slices. Using this experimental system, we compared devices with three tip shapes and three different insertion speeds. Qualitative analysis of video images revealed several kinds of direct vascular damage, including displacement of luminal contents, rupture, breakage, and vessel dragging. These may all cause collateral damage to the surrounding nervous tissue. Damage to transcerebral arteries at times occurred over 100 μm from the insertion site, suggesting that initial damage to the neurovasculature may greatly impact the extent of the reactive responses. In addition, pial vessels were often carried into the neural parenchyma by the device. Algorithms for automated image analysis were developed to permit tracking of up to 100 interest points within each tissue sample during a single insertion. These measures permitted calculations of tissue deformation and maximum and effective strains resulting from insertion. Tip shape and insertion speed appeared to have independent effects. Insertion speed had a greater effect. Three distinct deformation patterns have been identified based primarily on insertion rate. Surprisingly, cortical surface features were one of the most influential factors affecting insertion damage; attempts to insert devices through pial blood vessels *ex vivo* resulted in severe compression. *In vivo* insertions through distributing arteries, precortical arteries, or pia alone resulted in differences in the magnitude of reactive responses at 1 and 6 weeks following insertion, as revealed by immunohistochemical labeling of thick tissue sections for laminin (vasculature), GFAP (astrocytes), Iba1 (microglia), and Nissl stain (neurons). These results will help guide future design of neural prosthetic devices and provide the groundwork for establishing safe insertion conditions.

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Feedback Control for a High Level Upper Extremity Neuroprosthesis

Dimitra Blana, Juan Gabriel Hincapié, Edward K.J. Chadwick, and Robert F. Kirsch

Department of Biomedical Engineering, Case Western Reserve University, Cleveland, OH

The purpose of this project is to develop a feedback controller for a high-level upper extremity neuroprosthesis. This controller will restore a range of arm movements to individuals with C3/C4 spinal cord injury who have lost voluntary control of almost the entire upper extremity. The users will generate commands for arm movements that will be used as inputs to the controller to generate the level of activation of the appropriate muscles. The controller will also compensate for errors caused by external disturbances and fatigue by using body-mounted sensors that will provide feedback on the position and orientation of the arm. This is necessary because due to the high level of injury, voluntary correction for errors in the performance of the neuroprosthesis is not possible.

The controller is being developed using a model-based approach. Since there is a large number of shoulder and elbow muscles that must be controlled in high tetraplegia, many of which generate moments about two or more degrees of freedom, purely experimental methods are inefficient and impractical. For this purpose, a musculoskeletal model of the shoulder and elbow has been developed, using SIMM (Software for Interactive Musculoskeletal Modeling, Musculographics, Inc.). It includes 28 muscles, 6 bones, and 5 joints, with a total of 9 degrees of freedom. The morphological and muscle contraction parameters were obtained from cadaver studies performed by the Van der Helm group in Delft[1]. To verify the model, arm movements and EMG signals were recorded from able-bodied subjects. The joint angles were used as inputs to a series of inverse dynamic simulations, and the output muscle activations were compared to the EMG patterns.

The model is being used as a substitute for the real human arm in the design of the feedback controller. The controller consists of an artificial neural network, which calculates the muscle activations when no disturbances are present, and a set of fuzzy rules that correct the activations according to the position and orientation feedback. The performance of the controller is being evaluated by placing it in series with the forward model. Given the desired arm kinematics, the controller produces the required muscle activations, which are then used as inputs to forward dynamic simulations performed by the model. The output and the desired kinematics are compared, and the error is used to optimize the controller.

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[1]Breteler Klein, C.W. Spoor, and F.C.T van der Helm: Measuring muscle and joint geometry parameters of a shoulder for modeling purposes. J Biomech 32: 1191-1197, 1999.

Physiological Measures of Cochlear Prosthesis Channel Interaction

Ben Bonham[1], Russell Snyder[1], John Middlebrooks[2], Stephen Rebscher[1], Steve Bierer[1], and Alexander Hetherington[1]

[1]Epstein Laboratory, Department of Otolaryngology-Head and Neck Surgery, University of California, San Francisco, CA
[2]Kresge Hearing Research Institute, University of Michigan, Ann Arbor, MI

Contemporary human cochlear implants (CIs) are multichannel devices. Each of these channels is thought to excite a unique restricted and tonotopically appropriate population of auditory nerve fibers, similar to populations excited by spectrally restricted acoustic stimuli. This is the basis for the processing strategies used in contemporary CIs. Psychophysical and clinical studies indicate that these devices provide many users with open-set speech reception. Our animal studies seek to understand the physiological mechanisms that underlie this performance.

Using deaf animal models and intracochlear electrodes that approximate commercial CI electrodes, we have shown that many factors influence the spatial (spectral) and temporal distribution of neural activity evoked in the central auditory system by CI stimulation. Among these factors are: the amplitude of stimulus pulses; the pulse waveform (symmetric biphasic or pseudomonophasic); the orientation and separation of the electrode contacts; the mode of stimulation (monopolar, bipolar, or tripolar); the relative location and timing of concurrently activated channels (AN populations); and the relative location and timing of previously activated channels. This poster describes the effects of cochlear electrode position and stimulating mode on the distribution of neural activity in the inferior colliculus evoked by electrical stimulation. In some cases, the patterns of activation approximate those that are evoked by tonal acoustic stimuli, while in other cases they are significantly different.

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A Preliminary Clinical Study Using RF BION® Microstimulators To Facilitate Upper Limb Function in Hemiplegia

J.H. Burridge[1], R. Turk[1], S.V. Notley[1], G. Cosendai[2], O. Sparrow[1], and R. Davis[2]

[1]SOHPRS, University of Southampton, United Kingdom
[2]Alfred Mann Foundation, Santa Clarita, CA

About 85% of stroke survivors regain the ability to walk, whereas only 14% regain useful upper limb function. Learned non-use may be a factor; as in walking, the hemiplegic leg is forced into use, whereas upper limb tasks may be performed single handed.

Evidence for neuroplastic changes in response to augmented therapy in animal studies is now demonstrated in humans. Also, paired associative stimuli associated with function result in neuroplastic changes in cortical mapping. Furthermore, a recent review of functional electrical stimulation for upper limb function showed more improvement in motor control when stimulation was voluntarily activated. The work in each of these areas underpins the development of this study.

This investigational study, with six participants, tests the feasibility of using implanted radio-frequency BION® (RFB) micro-stimulators to improve motor relearning and recovery of arm and hand function following stroke. In the first case, five devices were implanted: one onto each motor-points/nerves (MP/N) of the medial (MHT) and lateral heads (LHT) of triceps to support elbow extension in reaching; one onto each MP/N of the extensor carpi ulnaris (ECU) and extensor carpi radialis (ECR) for wrist extension; and one, adjacent to the posterior interosseous nerve (PIN), to open the thumb and fingers. Programmed sequences have been designed to facilitate reaching (MHT and LHT); opening of the hand (PIN, ECR, and ECU); and grasping, by switching off the PIN so that the subject can use their own activity to grasp an object, while grip is strengthened by the maintained activation of the wrist extensors. Switching off the elbow extensors enables the object to be brought towards the body, and switching on the PIN allows the object to be released. Fixed times for each activity sequence are programmed. During the project, sensors will be integrated into the system so that activity sequences are triggered appropriately. For example, the program could be initiated by an EMG signal from anterior deltoid, extension of the wrist, opening of the hand by detection of elbow angle, and grasping—switching off the finger and thumb extensors—by a signal from a force-sensitive mat that detects when the subject touches an object resting on it. A ‘take-home system’ is being developed. Changes in function will be measured using standardized tests; changes in spasticity and motor control will be measured objectively using a specially designed and validated system.

STIMEXPLORER: Interactive Visualization Software for Deep Brain Stimulation Parameter Selection

Christopher R. Butson[1], Christopher B. Maks[1], Angela M. Noecker[1], Scott E. Cooper[2], Jaimie M. Henderson[3], and Cameron C. McIntyre[1,2]

[1]Department of Biomedical Engineering, Cleveland Clinic Foundation, Cleveland, OH
[2]Center for Neurological Restoration, Cleveland Clinic Foundation, Cleveland, OH
[3]Stanford School of Medicine, Department of Neurosurgery, Stanford, CA

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) has rapidly emerged as an effective treatment for Parkinson's disease (PD); however, programming DBS devices for maximal therapeutic benefit can be a difficult and time-consuming process. The fundamental purpose of DBS is to modulate neural activity with electric fields, and we have developed detailed computational models to accurately estimate the volume of tissue activated (VTA) as a function of the stimulation parameters (contact, voltage, pulse width, frequency). However, the computational power and computer science skills necessary to effectively implement such models are not available to most clinicians. Therefore, we have developed a Windows-based, clinician-friendly software package (STIMEXPLORER) intended to aid the postoperative programming of STN DBS for PD. STIMEXPLORER uses precompiled results from our detailed diffusion tensor-based finite element models of DBS that explicitly account for the effects of electrode capacitance, electrode impedance, and the 3D tissue electrical properties of the human brain. The stimulation results are coupled to 3D anatomical models of nuclei surrounding the electrode, and enable the clinician to interactively evaluate the effects of electrode location and stimulation parameter adjustments on the VTA. We have coupled our modeling results to clinical evaluations to establish a preliminary definition of the target VTA for STN DBS. Therefore, to customize the system to an individual patient, the clinician inputs the electrode position and orientation as well as the impedance of each electrode contact, and STIMEXPLORER provides a suggested theoretically optimal stimulation parameter setting. The intended benefits of using the STIMEXPLORER system are decreased time and effort needed to adjust the stimulation parameters to achieve acceptable clinical results from the therapy. In addition, STIMEXPLORER may decrease the level of intuitive skill necessary to perform DBS programming, provide a teaching tool on the effects of DBS, and enable a degree of standardization in programming practices across centers. To address some of these questions, we have begun clinical evaluation of the accuracy and efficacy of DBS programming achieved with STIMEXPLORER compared to standard programming practice.

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Model-Based Analysis of the Effects of Electrode Impedance, Electrode Capacitance, and 3D Tissue Electrical Properties on the Volume of Tissue Activated by Deep Brain Stimulation

Christopher R. Butson and Cameron C. McIntyre

Cleveland Clinic Foundation, Department of Biomedical Engineering, Cleveland, OH

Deep brain stimulation (DBS) has rapidly emerged as an effective clinical treatment for a wide range of neurological disorders; however, limitations exist in our quantitative understanding of the volume of tissue activated (VTA) during stimulation. Therefore, we have developed detailed computational tools to predict the neural response to DBS. Clinical DBS systems utilize voltage controlled, asymmetrical-biphasic stimulus waveforms, and are surrounded by a 3-dimensionally complex anisotropic-inhomogeneous tissue medium. These factors complicate accurate description of the electric field and subsequent prediction of the neural response to stimulation. To address these issues, we developed a 3D finite element model (FEM) of human DBS that incorporates diffusion tensor image (DTI) data to define the 3D tissue conductivities and a Fourier FEM solver to account for the capacitance of the electrode-tissue interface under voltage-controlled stimulation. The neural response to DBS is then predicted by coupling the electric field data from the FEM to multi-compartment neuron models surrounding the electrode. We evaluated the impact of electrode capacitance, electrode encapsulation, and 3D tissue electrical properties on the VTA. Our results show that each of these factors substantially affects neural activation. Electrostatic models that ignore electrode capacitance overestimate VTAs by ~20% compared to Fourier FEM-based voltage-controlled stimulation with typical therapeutic stimulation parameter settings. In addition, failure to account for electrode encapsulation and impedance values representative of clinical DBS result in an additional overestimation of the VTA by ~35%. Finally, incorporation of DTI-based 3D tissue electrical properties transform the VTA from spherical to a complex volume shape distorted by surrounding fiber tracts. The combination of all these effects can overestimate the spread of stimulation by 2-3 mm relative to more simplistic models. Therefore, attempts to make quantitative correlations between stimulation parameters and behavioral measurements on a patient-by-patient basis should account for the effects of electrode capacitance, electrode impedance, and 3D tissue electrical properties.

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Simulating Stimulation Fields Including the Electrode-Electrolyte Interface

D.R. Cantrell[1], R.S. Ruoff[2], and J.B. Troy[3]

[1,3]Neuroscience Institute, Northwestern University, Evanston, IL
[2]Mechanical Engineering Department, Northwestern University, Evanston, IL
[3]Biomedical Department, Northwestern University, Evanston, IL

Neural stimulation with implanted microelectrodes is important for both the advancement of basic neuroscience research and for the development of sensory prostheses. Spatially confined electrical stimulation of small groups of cells can be achieved with electrodes of either monopolar or bipolar designs. For the development of stimulating electrodes of high spatial resolution, the electric field created by a stimulus must demonstrate both a tight spatial confinement to allow for the activation of a minimal number of cells and also a high degree of uniformity to minimize the tissue damage that may be caused in regions of high current density. However, the localization and distribution of current density and electric field strength around the electrode during a stimulus remains poorly understood. We sought to compare the localization and uniformity of electric fields surrounding monopolar and concentric bipolar electrodes and to determine how the incorporation of a high impedance electrode-electrolyte interfacial layer into the model affects these results.

To address these aims, finite element simulations were run in the FEMLAB modeling environment. Quasi-static time-harmonic analyses were performed on models of conical monopolar and disk-shaped concentric bipolar electrodes submerged in a homogeneous physiological saline solution. Models were constructed with and without a thin layer placed at the surface of the metal electrode that possessed electrical properties representative of the complicated electrode-electrolyte interface. Stimulus potentials applied to the electrode were sinusoidal with amplitudes ranging from 0.1 V to 1 V and frequencies ranging from 1 Hz to 10 kHz. Visualization of the electric phenomena surrounding the stimulating electrodes was achieved by plotting the electric potential, the current density, the amplitude of the electric field, and the gradient of the electric field from the calculated solutions.

Modeled fields can be extremely local, suggesting that neural stimulation at high spatial resolution is possible with an appropriate electrode configuration.

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Improving Brain Tissue Integration of the Neural Probes Through Surface Immobilization of Biomolecules

Erdrin Azemi Charley, William R. Stauffer, Carl F. Lagenaur, and X. Tracy Cui

University of Pittsburgh, Pittsburgh, PA

Topic area: Neural Prosthesis

Silicon-based implantable neural electrode arrays are known to experience failure in long-term recording. Surface modification of these arrays is needed in order to improve their biocompatibility and integration within the host brain tissue.

The biomolecules, L1 and laminin, are immobilized on the silicon surfaces to promote attachment and growth of neurons. L1, a cell adhesion molecule expressed in developing CNS and PNS, is known to specifically promote neurite outgrowth and neuronal survival. Laminin, an extracellular matrix protein that interacts with a variety of cell types, is known to be an excellent substrate for neuronal attachment and growth. Silicon dioxide-coated wafers were used to mimic the surface of the neural probes in the *in vitro* model. After cleaning, silane chemistry and coupling agent, 4-Maleimidobutyric acid N-hydroxysuccinimide ester (GMBS), were used to covalently bind the biomolecules on the silicon surfaces. After immobilizing the biomolecules, polyethylene glycol (PEG)-NH_2 was used to inactivate the reactive GMBS and to inhibit nonspecific protein or cell-surface interactions. Primary neurons and astrocytes were plated on the modified surfaces. Both L1 and laminin promoted neuronal growth, with the L1-immobilized surfaces showing a better neurite outgrowth than the laminin-immobilized surfaces ($p<0.05$). In the astrocyte culture, laminin-immobilized surfaces promoted astrocyte growth, while L1-immobilized surfaces were not permissive to astrocyte growth. Based on the *in vitro* results, L1 was a better candidate for promoting specific neuronal ingrowth to the neural implant, while minimizing attachment of glial and other cell types.

Michigan probes were used for the *in vivo* studies. After immobilization of the L1 biomolecule, the probes were implanted randomly in the left and right cortex of mature rats, with unmodified and PEG-immobilized probes as controls. After 4 weeks, the rats' brains were sectioned, immunofluorescently stained, and analyzed for neurons, astrocytes, and microglia around the probe insertion site. A similar enhanced intensity of astrocytes was observed around the insertion site of the unmodified, PEG-immobilized, and L1-immobilized probes, indicating the common host glial-scar reaction to the implant. However, while a decreased neuronal density was seen around the control sites, this was not observed around the L1-immobilized probe site. This suggests that the immobilized L1 biomolecule improved survivability of neurons around the insertion site, and in some cases promoted neurite ingrowth toward the implant. Better neuronal density around the neural probes is necessary and beneficial for obtaining stable and high-quality neural signals. Future work will involve testing the long-term recording performance of these probes modified with L1.

Biphasic Pulse Signal Coding for Neural Recording

Du Chen, John G. Harris, and Jose C. Principe

Department of Electrical and Computer Engineering, University of Florida, Gainesville, FL

Topic area: Brain-Computer/Machine Interface

Many data acquisition systems are severely limited in terms of their power consumption and available data bandwidth. Implanted medical devices, remote sensors, and hearing aids are just a few examples of such power- and bandwidth-limited systems. This research focuses on implanted neural recording systems. The challenges for designers are how to best decrease power consumption and bandwidth while still preserving signal fidelity. Although the recorded sensor signal is typically analog, post-processing algorithms are completely digitally based, which raises the need of translating the analog signals to digital representations through ADCs.

We have previously demonstrated the IF (Integrate-and-Fire) signal representation for neural signal coding and transmission. In this technique, the regulated analog signal is passed through an IF neuron and the information is "losslessly" encoded into an asynchronous pulse train. The pulse train is compatible with digital logic circuits for subsequent processing. This coding method has the advantages of low power consumption and simpler front-end circuit design; however, the analog signal must be made strictly positive by adding a DC bias. Overall power will be wasted since the signal has to be shifted up by the worst case, which is the most negative possible value of the signal. A problem with this approach is that this DC bias will continuously produce spikes even when the original signal is in an "idle" state, during which there is no interesting information. The new biphasic technique eliminates the DC bias by employing two IF neurons that encode positive and negative signals, respectively. In this way, the IF neurons will not respond to the signal when the amplitude is small.

The biphasic pulse signal coding technique is in sharp contrast to conventional uniform sampling techniques since they must spend the same power and bandwidth on noise regions as they do in the spike regions. We have successfully simulated the biphasic coding on neural recordings with 25 kHz sample rate from Sprague-Dawley rats. We have shown that pulse rates as low as 6 kHz can be achieved while still preserving the details of the neural spike shapes. This sub-Nyquist rate sampling is achieved by reduced pulse rate in the noise regions. Finally, an ultra-low power, low-noise amplifier with biphasic pulse coding is under design for a custom analog VLSI chip.

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Complete System for Differential Cortical and Hippocampal Recording With Acceleration Sensitivity and Isolated Stimulation

Nick Chernyy[1,2], Nathalia Peixoto[1,2], Sridhar Sunderam[1,2], Jonathan P. Mason[1,2], Steve L. Weinstein[4], Steven J. Schiff[1,3], and Bruce J. Gluckman[1,2]

[1]Krasnow Institute for Advanced Study, George Mason University, Fairfax, VA
[2]Department of Physics and Astronomy, George Mason University, Fairfax, VA
[3]Department of Psychology, George Mason University, Fairfax, VA
[4]Children's National Medical Center, George Washington University, Washington, DC

Topic area: Brain Computer/Machine Interfaces

Prerequisites for an adaptive seizure control are (1) high-fidelity neurological data from the model animal for behavioral-state analysis and seizure identification, and (2) a method for delivering precise, isolated external stimuli. We have developed a recording system with a compact, micropower headstage that does both cortical and depth EEG recordings as well as head acceleration recordings. We have also developed the supporting hardware to interface this headstage to a commodity PC running commercial acquisition and control software.

The design specifications for this project were to (1) measure the differential cortical EEG signal from two pairs of screw electrodes, (2) measure hippocampal depth recordings from two pairs of bipolar electrodes, (3) deliver bipolar stimulation with both voltage feedback and current monitoring, and (4) record biaxial acceleration of the animal's head. A headstage was designed, consisting of two printed circuit boards (PCBs) which were about 1.5cm^2 in area each. These PCBs contained the first set of differential amplifiers in addition to stimulation voltage monitoring ICs and the MEMS accelerometer. Since these ICs were mounted close to the actual electrodes, the differential signal gave a good signal-to-noise ratio after amplification with minimal filtering on the animal's head. As a result of various design decisions and IC selection, we were able to meet these monitoring requirements while drawing 15 mW of power off +/- 2.5V rails. Secondary amplification and filtering was then done using a commercial amplifier to place all of the signals, with good voltage resolution, within the input range of the PC acquisition hardware. An optically coupled isolated stimulator was also designed, which would be voltage-programmed and provide low-capacitance, battery-powered output. Finally, hardware was developed to provide clean power to all of the systems involved, do stimulation current monitoring, and provide a direct interface to the PC acquisition hardware.

These systems were used in multiple runs for 10 days at a time per animal, and the data collected have been used in several associated research projects. Due to low power requirements, the stimulation system was powered off of a pair of standard AA batteries over the period of the experiment, and the headstage could potentially be powered by batteries as well.

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An Analysis of Cochlear Implant Elicited Stapedial EMG Recordings in Rats

Ryan Clement, Oneximo Gonzales, and Kunal Paralikar

Pennsylvania State University, Philadelphia, PA

Topic area: Auditory Prosthesis

The electrical stapedius reflex (ESR) threshold, detected by acoustic impedance changes at the eardrum, has been shown to be correlated with behavioral comfort levels established by cochlear implant recipients. However, reports suggest acoustic impedance changes are typically not detectable in 30-40% of patients. The objectives of this study were to develop an animal model and investigate the characteristics of the stapedius muscle electromyogram (SEMG) signal elicited by a cochlear implant as an alternative measure of ESR activation. Hand-fabricated tungsten bipolar microwire electrodes were placed into the stapedius muscle cavity of rats to record the SEMG signal. Rats were also implanted with multichannel intracochlear electrodes to electrically stimulate the auditory nerve. Maximum SEMG potentials ranged from 20 μV to greater than 500 μV, with a mean value of 174 μV (8-42 dB SNR; mean: 24 dB). The dynamic ranges of the responses that reached saturation were approximately 10 dB, with lowest thresholds observed for wider pulse widths and greater electrode separations. The electrical auditory brainstem response (EABR) threshold was 5.6 dB lower than the ESR threshold on average, but the standard deviation was relatively high (2.4 dB). Furthermore, the relationship between the EABR and ESR response growth curves were variable across animals and stimulation modes, suggesting that the EABR and ESR could provide independent information for objective cochlear implant fitting. Postoperative SEMGs were recorded in several animals, including one animal for up to 63 days. We are currently working on implementing an artifact rejection amplifier in the recording stream to enhance SEMG recording during high-rate stimulation and offer better comparison with the compound action potential. A more optimal SEMG electrode design integrated with cochlear implant telemetry would make this a feasibility strategy for measuring ESRs in cochlear implant users postoperatively. In addition to potentially higher ESR detection rates without the need for anesthesia, in the future this signal could be implemented as feedback to modulate stimulus levels “on line” to potentially improve speech recognition during vocalization and noise.

Charge-Injection Proprieties of Poly(ethylenedioxythiophene) Coatings for Neural Stimulation Electrodes

Stuart F. Cogan[1], Dharmasena Peramunage[1], and Philip R. Troyk[2]

[1]EIC Laboratories, Inc., Norwood, MA
[2]Illinois Institute of Technology, Chicago, IL

Microelectrodes for neural stimulation are characterized by a charge-injection capacity defined as the maximum charge that can be injected into tissue without the electrode potential exceeding limits of reversible operation. For platinum and iridium oxide electrodes, these limits are defined by water electrolysis (-0.6 to 0.8 V vs. Ag|AgCl) and result in maximum charge-injection capacities of about 0.3 mC/cm^2 and 4 mC/cm^2, respectively. In the present work, the charge-injection capacity of poly(ethylenedioxythiophene) (PEDOT), a polymer with intrinsic electronic conductivity, is investigated and compared with that of platinum and activated iridium oxide (AIROF).

PEDOT was deposited onto gold disc electrodes (geometric area 7,850 μm^2) as well as cone-shaped platinum-iridium (Pt-20Ir) penetrating microelectrodes (typically 2,000 μm^2) by electro-polymerization from an aqueous solution containing 0.05 M EDOT (monomer), 0.04 M polyethylene-10-laurylether surfactant, and 0.1 M poly(styrenesulfonate) dopant. Electro-polymerization protocols involving potential cycling and galvanostatic oxidation were investigated. PEDOT films were characterized by scanning electron microscopy (SEM), cyclic voltammetry, electrochemical impedance spectroscopy, and potential transient measurements during current pulsing. All electrochemical measurements were made in an electrolyte containing the principal inorganic constituents of interstitial fluid at 37^{o}C and pH=7.4.

SEM revealed uniform and compact PEDOT on both the disc and cone electrodes. The amount of PEDOT deposited was quantified by integrating the cathodic current during cyclic voltammetry at a sweep rate of 50 mV/s between potentials of –1.0 V and 0.6 V vs. Ag|AgCl, the limits for reduction and oxidation of water on PEDOT, respectively, and ranged from 20-80 mC/cm^2. The 1 kHz impedance of uncoated disc electrodes was reduced by a factor of 20 from 56.5 kΩ to 2.64 ±0.37 kΩ (±s.d., n=9) after PEDOT coating. The charge-injection capacity for cathodal-first current pulses varied from ~10 mC/cm^2 for 0.2-ms pulses to >25 mC/cm^2 for 0.8-ms pulses, using a negative potential limit of –0.6 V. The PEDOT charge-injection capacity exceeds that of AIROF by a factor of >3 and of platinum by a factor of >30. This high-charge capacity is a consequence of the high-rate capability (50 A/cm^2 in 0.2-ms pulses) of the redox processes in PEDOT that permit over 60% utilization of the available polymer in pulse width of 0.8 ms.

PEDOT coatings electro-deposited onto gold and PtIr electrodes allow significantly higher levels of charge-injection, without water electrolysis, than platinum or iridium oxide. The stability and biocompatibility of PEDOT under conditions of chronic *in vivo* pulsing remain to be determined.

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Training Individuals to Use Their EEG/ECoG Signals to Command an Upper Limb Neuroprosthesis

Thomas M. Cowan[1] *and Dawn M. Taylor*[1,2]

[1]*Department of Biomedical Engineering, Case Western Reserve University, Cleveland, OH*
[2]*Louis Stokes Cleveland VA Medical Center, Cleveland, OH*

Topic area: Brain-Computer Interface

Our colleagues at the Cleveland Functional Electrical Stimulation (FES) Center are developing and implementing FES systems for restoring upper limb movements in people with spinal cord injuries (SCI). For people with SCIs at the C5/C6 level, EMG activity or external shoulder joysticks can be used to control hand function. However, FES systems to restore full arm and hand movement in individuals with injuries at the C4 level and above are more problematic to command. Individuals with higher level injuries have less function that can be used as command signals, yet they require more command signals to compensate for the greater loss of function.

One solution is to obtain signals directly from the source of volitional control, the brain. We are currently in the process of evaluating electroencephalograms (EEGs) and electrocorticograms (ECoGs) as potential command sources for an upper-limb FES system for people with SCI at the C4 level and above. We are determining the number and resolution of independent command signals a person can learn to produce through willful modulation of various frequency bands recorded via each of these technologies. We are recruiting people with epilepsy who are being monitored with subdural grid electrodes and have some electrodes located over motor-related brain areas. We are also conducting parallel evaluations in able-bodied and SCI subjects using scalp surface EEGs. In this study, subjects attempt to control the movements of a virtual arm/hand in an increasing number of dimensions. We are using a coadaptive decoding algorithm to rapidly identify an effective decoder for controlling the virtual arm/hand. The algorithm makes no assumptions on how the brain will encode movement, which is appropriate for both SCI subjects whose brain patterns may have changed after injury and for epilepsy patients with electrodes over a mix of motor and nonmotor areas. The algorithm rapidly adapts to enable naïve subjects to control the virtual hand with no prior training. We are working to increase stability of the adaptive decoding functions by developing real-time methods to remove EMG artifacts and by optimizing adaptation rates for EEGs and ECoGs. We are also evaluating effective mapping functions that can robustly translate noisy command signals into effective limb commands for reaching and grasping movements.

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Variability in the Subthalamic Nucleus and Red Nucleus Relationship in Parkinson's Disease: Implications for Targeting

Shabbar F. Danish[1, 2], Jurg Jaggi[1], Jason T. Moyer[2], Leif Finkel[2], and Gordon H. Baltuch[2]

[1]Department of Neurosurgery, University of Pennsylvania, Philadelphia, PA

[2]Department of Bioengineering, University of Pennsylvania, Philadelphia, PA

Background: An understanding of the relationships between the anterior commissure-posterior commissure line (AC-PC), the subthalamic nucleus (STN), and the red nucleus (RN) is imperative to ensure accurate targeting for deep brain stimulation. These relationships are incompletely understood. We examine the location and relationships of the subthalamic nucleus and the red nucleus to the AC-PC line and each other in order to provide a greater understanding of their utility when targeting STN.

Methods: A total of 52 STN and RN in 26 patients with Parkinson's disease were evaluated on T2-weighted MR images (1.5-mm slices). The anterior and posterior commissures and the border coordinates of STN and RN were derived using frame coordinates. The distances from the midcommissural point to the centers of STN and RN, diameters for each nuclei, and the distances between each nuclei were calculated in the x, y, and z planes. Right vs. left variability and dependence on AC-PC length were examined.

Results: The mean AC-PC length was 26.1 $\pm$ 1.3 mm. Subthalamic nucleus center point distance from the midcommissural point was highly variable: 8.3 to 11.7 mm in the x plane, -3.1 to 2.6 mm in the y plane, and 1.3 to 5.4 mm in the z plane. The red nucleus distance was also very variable: 2.2 to 5.8 mm in the x plane, -3.6 to -8.4 mm in the y plane, and 3.3 to 9.5 mm in the z plane. The relationship between STN and RN was very variable in all planes: 1.0 to 4.1 mm in the x plane, 0.2 to 4.8 mm in the y plane, and -3.0 to 2.3 mm in the z plane. There was no significant difference within a given patient between right- and left-sided locations. There was no correlation between the distances or dimensions of STN and RN to the length of the AC-PC line. There was no significant correlation between the AC-PC length and the relationships between STN and RN.

Conclusions: Although recent studies imply that the red nucleus can be used as a relatively constant marker for the position of STN, the present data suggests otherwise. These data indicate that a single-targeting method may be inadequate for any given individual patient, and that it is imperative to use multiple anatomical measurements when targeting STN for deep brain stimulation in Parkinson's disease.

High Frequency Subthalamic Stimulation Restores Order to Pallidal Firing Patterns

Alan D. Dorval[1], Gary S. Russo[2], Takao Hashimoto[3],
Weidong Xu[2], Jerrold L. Vitek[2], and Warren M. Grill[1]

[1]Department of Biomedical Engineering, Duke University, Durham NC
[2]Center for Neurological Restoration, Cleveland Clinic Foundation, Cleveland OH
[3]Third Department of Medicine, Shinshu University School of Medicine, Matsumoto, Japan

Topic area: Deep Brain Stimulation

Deep brain stimulation (DBS) alleviates motor symptoms in persons with movement disorders. The mechanisms of DBS are poorly understood, however, limiting optimization and development. For treatment of Parkinson's disease, high-frequency stimulation (HFS) of the subthalamic nucleus (STN) alleviates symptoms similarly to surgical STN lesion. While lesion abolishes STN output, recent work demonstrates that HFS increases the firing rates of STN efferent fibers. In this work, we address how HFS and lesion yield similar behavioral results via opposite effects on STN firing rates.

We hypothesize that movement disorder symptoms originate in the disordered neural firing patterns of the basal ganglia, and that HFS restores order to these firing patterns. We analyzed the effects of symptom-relieving HFS and symptom-exacerbating low frequency stimulation (LFS) of the STN on unit activity in the globus pallidus (both GPi and GPe as effects were similar) and pallidal-receiving areas of the thalamus in the MPTP-primate model. In addition to significantly ($p<.002$) increasing the firing rate of GP neurons by 21±33 Hz (mean±std; 52/69 cells), HFS also significantly decreased the firing pattern entropy (a quantitative measure of disorder) by 0.20±0.45 bits/spike (45/69 cells). Pallidal-receiving thalamic cells were evenly divided into those in which HFS increased (20/41 cells) or decreased (19/41 cells) firing pattern entropy. In contrast, LFS had no net effect of firing rate, but significantly increased firing pattern entropy in GP neurons by 0.25±0.44 bits/spike (135/147 cells), and in thalamic cells by 0.74±0.48 bits/spike (72/76 cells). These results suggest that symptom modification is mediated through changes in the regularity of GP firing patterns, which are synaptically propagated to thalamus where they impact motor output. Hence, the surgical procedures of lesion and DBS may share a common mechanism: lesioning removes the disordered region altogether, while high frequency DBS forcibly regularizes regional output.

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Volitional Surface EMG Based Control of FES-Assisted Ambulation After Incomplete Spinal Cord Injury — A Single Case Feasibility Study

Anirban Dutta[1] *and Ronald Triolo*[1,2]

[1]*Department of Biomedical Engineering, Case Western Reserve University, Cleveland, OH*
[2]*Department of Orthopedics, Case Western Reserve University, Cleveland, OH*

The volitional surface electromyogram (sEMG) can be used to drive the functional electrical stimulation (FES) of the less-functional synergists during a cyclic activity like gait. The volitional lower-body sEMG in an incomplete spinal cord injured (iSCI) subject during FES-assisted over-ground ambulation was studied to develop an sEMG-based FES controller.

The iSCI subject (age 23 years, C7 ASIA C), who volunteered for the study, has an implanted 8-channel FES-stimulator (IRS 8), driven by an external control unit (UECU) developed by the Technology Development Laboratory (TDL) at the Cleveland FES Center (fescenter.case.edu). Volitional sEMG was collected bilaterally from anterior tibialis, quadriceps, hamstrings, calf, and gluteal muscle groups during FES-assisted, finger-switch triggered gait to identify a muscle set that has enough volitional sEMG information. The sEMG was blanked to prevent stimulation artifact, pre-amplified and low-pass (anti-aliasing, 1,000 Hz) filtered before being sampled at 2,400 Hz by the data-acquisition card. The rectified sEMG was normalized by the maximum value during the gait cycle and filtered by a moving average window of 150 ms.

The partially paralyzed medial gastrocnemious (mGas, bilaterally) was selected for the sEMG signal. The push-off phase of the gait was identified using mGas's sEMG signal and was used to trigger the FES-assisted swing phase of the ipsilateral leg. The average sEMG magnitudes during 150 ms just prior to toe-off (found using insole FSRs) from a set of 80 gait-cycles were used to calculate the probability density function for each muscle. The calculated probability density function was used to estimate the membership function for the fuzzifier. A threshold was selected to minimize the false positives using a receiver-operating-characteristics curve to get a binary output (i.e., the trigger signal) from the fuzzy-inference system. The FES controller was developed in Simulink (The MathWorks, Inc.) and ran on xPC target PC. The UECU was driven by the xPC target PC in real-time using the software toolkit developed by TDL. The time-period between the end of the swing-phase of the contralateral limb and start of the swing-phase of the ipsilateral limb (i.e., the double-support phase) was used to determine the duration of the swing-phase using extrapolated able-bodied data. This provided a more natural way of controlling the FES-assisted swing-phase as compared to the finger-switch for the subject who has below-normal finger function.

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Polyimide Microelectrode Arrays for a Retinal Prosthesis

Helmut Eckhardt[1], Stefan Ufer[1], Hossein Ameri[2], Tanapat Ratanapakorn[2], and James Weiland[2]

[1]Premitec, Inc., Raleigh, NC
[2]Doheny Eye Institute, University of Southern California, Los Angeles, CA

Although considerable progress has been made in the development of a functional retinal prosthesis, many hurdles remain before a long-term implant is feasible. The curved retinal surface, the delicate nature of the retinal tissue, and the mobility of the eye, all pose significant mechanical hurdles. The electrical properties of the interface represent equal challenges before stimulation of neurons, without thermal damage to the tissue, is achieved.

Substrate and insulation materials for retinal stimulators have to fulfill several requirements for acute and (especially) chronic implantation. They have to be stable in the physiological environment without any degradation, have to be nontoxic, and the design of the implanted device has to be "biomechanically safe" with a smooth geometry to prevent induced nerve trauma by sharp edges or insufficient flexibility. One of the most promising class of materials as substrate and as insulation layer for flexible retinal implants is polyimide. The insulation resistance and dielectric strength of polyimides are similar to silicon and conventional insulation materials with the added benefit of much higher flexibility. In addition, hybrid assemblies of polyimide-based electrode arrays and Si-based VLSI chips have been demonstrated.

The purpose of this Phase II SBIR is the development of a novel flexible integrated microelectrode array as an active neural interface to the retina of the human eye. The microelectrode arrays, interconnecting leads, and circuitry traces are all embedded and integrated on a single polyimide foil and encapsulated with proprietary multilayer insulating coatings made up of improved spin-on polyimides and thin (~300 nm) gas plasma polymer coatings. Our approach is based on the development of proprietary processes for spin-on polyimide coatings and a series of proprietary diamond-like carbon films (DLC) called A-coats™, which are deposited by plasma-enhanced chemical vapor deposition (PECVD) on top of the spin-on polyimide coatings. The surface properties of these DLC films can be engineered to yield hydrophilic or hydrophobic surface properties to improve biocompatibility. They exhibit excellent adhesion to most plastic substrates and metals, can be easily patterned, and show low moisture and oxygen permeabilities.

We have demonstrated through long-term soak tests that these multilayer structures perform well *in vitro* and protect the underlying microelectrodes in isotonic saline solutions and at the same time exhibit good biocompatibility. Novel flexible devices were designed and fabricated to create vision in both the central and peripheral visual field. These wide-field arrays were implanted in several dogs through a small scleral incision, thus minimizing the distortion in the eye. They conform well to the surface of the retina. Results for the *in vivo* testing of these arrays for biocompatibility and biomechanical safety will be reported.

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Brain-Computer Interfaces Using EEG and ECoG

Elizabeth A. Felton[1], J. Adam Wilson[1], Gerwin Schalk[4], Robert G. Radwin[1], Justin C. Williams[1,2], and P. Charles Garell[1,2,3]

[1]Department of Biomedical Engineering, University of Wisconsin at Madison
[2]Department of Neurological Surgery, University of Wisconsin, Madison Hospital, Madison, WI
[3]Department of Neurological Surgery, William S. Middleton VA Medical Center, Richmond, VA
[4]Wadsworth Center, New York State Department of Health, Albany, NY

Topic area: Brain Computer Interfaces

Brain-computer interface (BCI) technology has the potential to provide patients with severe motor disabilities greater independence and a higher quality life. BCIs take recorded brain signals and translate them into real-time actions; in this case, movement of a cursor on a computer screen. Training methods, mental effort, and workload will be significant factors in the success of BCIs as a means of communication and independence for individuals who rely upon them.

Nine subjects participated in the study: four able-bodied individuals with electroencephalogram (EEG) electrodes over sensorimotor cortex and five neurosurgery patients with implanted subdural electrocorticogram (ECoG) electrodes. Subjects were trained over multiple sessions to control a computer cursor with their brain signals. First, screening data were collected where subjects imagined movements or sounds when they saw a cue on the computer screen. Offline data analysis was performed to find signal features that corresponded to the imagery, and could potentially be modulated by the subject. Small segments of the chosen frequency band(s) were assigned to directions of cursor movement. Subjects then used their brain signals to move a cursor towards a target on a computer screen by controlling its vertical movement. BCI2000 software (Wadsworth Center, Albany, NY) was used for all experiments[1]. Accuracy, improvement on the task over time, and response to perturbations were methods of evaluating performance. Subjects also filled out questionnaires before and after each session as a measure of subjective mental effort.

ECoG subjects performed at >70% accuracy (average 84%) on a two-target task by the second testing session (total time ~30 minutes). With multiple sessions, ECoG subjects performed up to 100% accuracy for a two-target task and three subjects were able to perform at levels of accuracy at least twice that of chance for three- to eight-target tasks. EEG subjects performed at >60% accuracy (average 66%) on a two-target task by the third testing session (total time ~45 minutes). Three ECoG subjects had electrodes over the temporal or parietal cortex and attained cursor control at up to 100% accuracy for two- to eight-target tasks, despite the location away from motor areas. This finding suggests that brain areas not previously considered ideal for BCI control may be used for BCI purposes.

1. Schalk, G., et al., BCI2000: A general-purpose brain-computer interface (BCI) system. *IEEE Transactions on Biomedical Engineering*, 2004, 51(6): 1034-1043.

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An Introduction to the Neurotech Network

Jennifer French

Neurotech Network/The Society to Increase Mobility, Tampa, FL

Neurotechnology provides solutions quite different from conventional therapies and treatments for impairment disabilities and diseases. This technological field is changing so rapidly that doctors and clinicians are experiencing great difficulty keeping up with its advances, let alone finding the time to educate their patients. The Neurotech Network is a nonprofit organization established to help overcome this problem. The organization focuses on educating with unbiased information, communicating experiences, updating on advances, and advocating access for those persons with impairments who may benefit from the use of neurotechnology. While the organization does not rate, endorse, recommend, or prescribe any products, procedures, or services, it does provide relevant information so that those who may benefit from neurotechnology have the facts necessary to make informed decisions.

The incentive for forming the Neurotech Network was based on the recognition that there is a general lack of awareness epidemic regarding the availability and treatment methods possible using neurotechnology devices. It is the goal of the Neurotech Network to become the nerve center and the focal point for the exchange of information needed by those persons with impairments, their families, their caregivers, and relevant health care and medical professionals.

Neurotech Network has launched several educational resources since it's creation in 2003. Over 8,000 newsletters and e-newsletters addressing education resources are distributed on a quarterly basis. Neurotech Network, in conjunction with the Neurotech Business Report, is developing a searchable database containing products specific to various conditions and treatments. The resources are available on the www.NeurotechNetwork.org website, which is an expanding source of information. These approaches will not only further the awareness amongst the target groups, but will also help the development of the industry.

In the near term, Neurotech Network will develop and distribute in-service presentations for clinics and disability organizations, and related health care conferences; embark on a PR campaign to gain a presence for neurotechnology in the disability media; and conduct customer "use-and-need"-based research. Financial supporters of the Neurotech Network make it possible to provide these resources. There is still a need, particularly for those in neurotechnology research organizations, to contribute the necessary knowledge to help create quality resources.

We ask you to please visit us and learn more about our mission, projects, and those future resources needed to help people with disabilities regain their lives through neurotechnology.

The Neurotech Network operates under the license of The Society To Increase Mobility.

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Effects of Low and High Frequency Thalamic Stimulation on Spontaneous Cortical Local Field Potentials of Thalamocortical Rat Brain Slices — Studies With Multi-Electrode Arrays

Gajendiran Mahadevan[1], Eduardo A. Lima[1], Peter E. Konrad[1,2], C. Chris Kao[2], and Franz J. Baudenbacher[1]

[1]Department of Biomedical Engineering, Vanderbilt University, Nashville, TN
[2]Department of Neurosurgery, Vanderbilt University, Nashville, TN

Deep brain stimulation (DBS) of the ventral intermediate nucleus (VIM) of the thalamus is one of the effective treatment options for movement disorders such as Parkinson's disease and essential tremor. However, the exact mechanism by which high frequency stimulation-mediated suppression of tremor is poorly understood. In the present study, we used multi-electrode arrays (MEA), a noninvasive extracellular recording system by which an electrical activity of living cells in intact thalamocortical network neuronal tissue can be mapped at as many as 60 sites simultaneously.

Thalamocortical brain slices were prepared with a Vibratome at 350 μm thickness and the slices were incubated in ACSF for 2 hours before transferring to the MEA chamber. The slice was placed on the bottom of the MEA chamber (Multi Channel Systems, Reutlingen, Germany), and the spontaneous cortical local field potentials (LFPs) were recorded simultaneously from multiple MEA electrodes to map the spontaneous oscillations continuously. The spontaneous activity is as a result of intrinsic network interactions between the thalamic relay neurons, GABAergic reticular neurons, and cortical pyramidal cells. The MEA chamber was continuously perfused with oxygenated (95% O_2-5% CO_2) Mg^{2+} free or low Mg^{2+} ACSF. Stimuli (100 μs, 10, 50, 100, 150 Hz, 0-5 V, Medtronic DBS test stimulator) were delivered via a flattened 3389 lead placed on the top of the slice, and the responses were recorded using a Plexon multichannel recording system (up to 64 channels, Plexon, Inc., Dallas, TX).

The spontaneous cortical LFPs were inhibited by ventrobasal thalamic stimulation with increasing stimulus and stimulus frequency. The spontaneous cortical LFPs events are completely inhibited by non-NMDA receptors but not by NMDA receptors. In the presence of (-) bicuculline methiodide (10 μM), the cortical LFPs recorded from the somatosensory cortex of caudal thalamocortical brain slices were significantly reduced at 10 Hz, whereas a higher stimulation frequency (100 Hz) was needed to inhibit the cortical LFPs recorded from rostral thalamocortical brain slices. These results suggest that high frequency DBS-mediated inhibition of spontaneous cortical LFPs in the presence of $GABA_A$ receptors antagonists indicate the involvement of other than $GABA_A$-mediated inhibitory mechanisms and a differential regulation of these receptors at the thalamic level.

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A New Type of Neural Prosthesis

Liu Shi Gan, Troy Bornes, Allen Denington, and Arthur Prochazka

Centre for Neuroscience, University of Alberta, Edmonton, Alberta

Neural prostheses (NPs) are electrical stimulators that help to restore lost sensory or motor functions due to neural damage. Most existing NPs are either external to the body and deliver electrical pulses through surface electrodes attached to the skin over the target nerves, or internally implanted. Although both systems have been used successfully, each is associated with a number of disadvantages. External NPs tend to have poor selectivity, due to lack of proximity to the targeted nerves. Completely implanted systems are expensive, inaccessible for servicing and maintenance, and require sophisticated circuitry and design to ensure proper control of the device.

We now report a novel means of directing current from surface electrodes to one or more deep-lying nerves by implanting a passive conductor. The passive conductor comprises a metal pick-up terminal that is electrically connected by an insulated stainless steel wire to a conductive delivery terminal in a nerve cuff placed on the target nerve. An external stimulator is used to deliver stimulus current to the skin via a pair of surface electrodes, with the stimulating electrode, or cathode, placed overlying the subcutaneously implanted disc. When stimulus current is applied between the surface electrodes, the implanted pick-up electrode captures some of this current and diverts it through the implant to a target nerve. Ideally, the amount of diverted current is sufficient to stimulate the target nerve without causing discomfort or muscle contraction under the surface electrodes.

Both acute and chronic animal experiments have been conducted to show proof-of-principle, to characterize the system, and to ensure its safety before proceeding to human trials. The system was acutely implanted in four rats, two cats, two rabbits and one piglet, and chronically implanted in three cats. The system was found to successfully elicit a full range of controllable muscle contractions at current levels below those producing local muscle contractions. Threshold current for bipolar stimulation was about 30% lower than for monopolar stimulation. Wire resistance and skin thickness did not have any major effect on contraction thresholds. It was observed that both pick-up and surface electrodes can be quite small and remain optimally functional. Initially, chronic implants were unsuccessful due to wire breakage, but newer reinforced conductors remained functional over 9 months.

Selectivity of stimulation through surface electrodes is greatly improved with the stimulus router. Graded control of muscle contraction is achievable with the system, and this is essential for functional electrical stimulation. The experimental results obtained suggest that the stimulus router system is a cost-effective alternative to current NP models.

This study was funded by the Alberta Heritage Foundation for Medical Research and Canadian Institutes of Health Research.

Funding Surgically Implanted Device Trials in the United States: Recommendations of the Clinical Research Funding Task Force

Karen G. Gervais[1], J. Eline Garrett[1], Dorothy E. Vawter[1], Angela Witt Prehn[1], Raymond G. De Vries[2], Timothy Q. McIndoo[1], and Thomas B. Freeman[3]

[1]Minnesota Center for Health Care Ethics, Minneapolis, MN
[2]St. Olaf College, Northfield, MN
[3]University of South Florida, Tampa, FL

Topic: Improving Funding Infrastructure for Research on Surgically Implanted Devices

The infrastructure supporting clinical trials of surgically implanted, significant-risk medical devices (surgical device trials or SDTs) is deficient, through the fault of no single stakeholder engaged in the devices' development, study, or use. Through focus groups and interviews of neurosurgical researchers, we learned that funding negatively impacts the types, quality, ethical caliber, and social value of SDTs. Respondents expressed numerous concerns about the sufficiency of funding, maldistribution of funding responsibility, and inefficient use of scarce research dollars. Guided by researchers' concerns and building on the Institute of Medicine's Clinical Research Roundtable, our team convened the public/private Clinical Research Funding Task Force (CRFT), seeking stakeholder consensus on improvements to the national funding infrastructure for SDTs. CRFT met quarterly for 2 years ending in 2004 and comprised:

- Academic health centers and researchers
- Device manufacturers
- Federal and State agencies that sponsor or regulate clinical research or health care
- Other health care providers
- Patient advocacy groups and private foundations
- Private and public third-party payers.

Moderators used case studies and audience response technology to facilitate CRFT's analysis and consensus-building process. Recognizing that all stakeholders have interests in a vital SDT funding infrastructure, CRFT calls for the establishment of a novel, collaborative funding arrangement. Public and private stakeholders would equitably contribute funds and other resources—some by mandate and others voluntarily—to a collaborative funding pool. In decisions about which SDTs to support with these pooled resources, stakeholders groups would be represented in proportion to their contributions. CRFT identifies with some specificity the relative roles various stakeholder groups should play in funding SDTs for different stages of research, prioritizing post-FDA approval device trials. CRFT also recommends regulatory incentives for conducting high-quality SDTs, improved training of surgical device researchers, and heightened editorial standards for publishing surgical device research. CRFT addresses a much-neglected area of the clinical research enterprise that is of concern to surgical researchers. Its recommendations may inform policy dialogue concerning funding for other kinds of clinical research, and our process may be instructive to those involved in developing consensus on contentious issues among disparate stakeholders.

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Controlling lower urinary tract function with electrical stimulation in the central and peripheral nervous system

Robert Gaunt, Vivian Mushahwar and Arthur Prochazka
Department of Biomedical Engineering and Center for Neuroscience, University of Alberta, Edmonton, AB

Lower urinary tract dysfunction occurs as a result of spinal cord injury and a wide variety of other conditions of both neurogenic and non-neurogenic origin. This disruption of normal control can lead to a decreased quality of life, serious medical complications and high health care costs. After spinal cord injury, concomitant contraction of the bladder and sphincter prevents voiding and can lead to elevated intravesical pressures and upper urinary tract deterioration.

We examined the use of intraspinal microstimulation (ISMS) to achieve coordinated bladder contractions and sphincter inhibition to allow voiding after spinal cord injury. Previous results from acute experiments suggested that ISMS may be an effective means to accomplish this, so we examined ISMS in chronically implanted animals. Arrays of 12-16 microwires manufactured from 30 μm platinum-iridium wire were implanted in sacral segments S1 and S2 of spinally intact cats. One group of electrodes targeted the sacral parasympathetic nucleus which contains bladder preganglionic neurons. The other group targeted the dorsal gray commissure which contains interneurons with inhibitory projections to sphincter motoneurons. It was hypothesized that simultaneous stimulation in these two regions would elicit bladder contractions and inhibit the sphincter, resulting in micturition. In some animals, both bladder contractions and sphincter inhibition were achieved, but without significant micturition. In many cases, only small increases in bladder pressure were elicited with many electrodes eliciting nonspecific hindlimb movements and sensory responses. This is likely due, in part, to physiological issues surrounding the neurons in the dorsal gray commissure, initial electrode placement and electrode migration over time. Therefore, the methods utilized in this project would need to be significantly refined before a clinically viable ISMS-based neuroprosthesis for bladder control could be implemented.

Meanwhile, we investigated a new stimulation technique involving routing current from surface electrodes to nerve cuffs circumscribing the pudendal nerves and sacral roots via a passive implant. A wide range of stimulation parameters and paradigms were explored during acute experiments in adult male and female cats under isoflurane anesthesia. Low-frequency stimulation of the pudendal nerve was used to contract the sphincter. Large, maintained bladder contractions were also elicited using this technique with nerve cuffs placed on the S1-S2 sacral roots. These preliminary data suggest that existing stimulation paradigms could be combined with stimulus routing techniques to form the basis of a simple neuroprosthesis for bladder control.

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A Wideband Power-Efficient Inductive Wireless Link for Implantable Biomedical Devices Using Multiple Carriers

Suresh Atluri and Maysam Ghovanloo

Department of Electrical and Computer Engineering, North Carolina State University, Raleigh, NC

An inductive link between two magnetically coupled coils that constitute a transformer is the most common method to wirelessly transmit power and data to implantable biomedical devices that have relatively high power consumption, such as neuromuscular stimulators, cochlear implants, and visual prostheses. Neuroprostheses that substitute sensory functions also need sizeable amounts of real-time data to interface with a large number of neurons by means of tens to hundreds of stimulating sites that are driven simultaneously through multiple parallel channels. The wireless link should be robust enough not to be affected by patient's motion artifacts or minor coils misalignments. A back telemetry link is also needed for implant power regulation, stimulating sites impedance measurement, and recording the neural response for accurate electrode placement and stimulation parameter adjustments.

Therefore, high power transmission efficiency, high data transmission bandwidth, magnetic coupling insensitivity, and back telemetry are the major wireless link requirements in the design and implementation of a large class of implantable biomedical devices. While these requirements are individually attainable, they have not been achieved concurrently with traditional techniques. The reason is that there are conflicting constraints involved in achieving high performance in two or more of the above system requirements.

The wireless link operating frequency, also known as the carrier frequency, is one of the most important parameters of an inductive link, which affects all other system specifications. Traditionally, a single-carrier frequency has been used for (1) inductive power transmission, (2) forward data transmission from outside to the implanted device, and (3) back telemetry from the implanted device outward. In this research, we are using three carrier signals at three different frequencies and amplitude levels: (a) low-frequency, high-amplitude ($f_P < 1$MHz) for power transmission; (b) medium-frequency, medium-amplitude ($f_{FD} \sim 50$MHz) for forward data link; and (c) high-frequency, low-amplitude ($f_{BT} > 1$GHz) for back telemetry. These frequencies are optimal for the above three major functions and we can effectively isolate many of the competing parameters in the design of a wireless link. Therefore, we expect to achieve a high performance in all of the aforementioned system requirements.

The research presented here is aimed at developing a robust, power-efficient, wideband, bidirectional wireless link using multiple carrier frequencies. The new link will be utilized in development of a prototype neuroprosthetic test-bed for a mid-brain auditory implant. The prototype neuroprosthesis will be tested *in vitro* to evaluate the multi-frequency wireless link performance. Then it will be used in short-term *in vivo* experiments through collaboration with the University of North Carolina, Department of Otolaryngology, Head, and Neck Surgery.

This work is supported by the Faculty Research and Professional Development Program, Division of Research Administration, North Carolina State University.

DEVELOPMENT OF A SWITCHED-CAPACITOR BASED NEUROSTIMULATING SYSTEM FOR LOW-POWER HEAD-MOUNTED DEEP BRAIN STIMULATORS

Maysam Ghovanloo[1], *Oleg Favorov*[2], *Richard W. Murrow*[3], *and Mark Tommerdahl*[2]

[1]Department of Electrical and Computer Engineering, NC State University, Raleigh, NC
[2]Joint Department of Biomedical Engineering, UNC/NCSU, Raleigh, Chapel Hill, NC
[3]Department of Neurology, University of North Carolina, Chapel Hill, NC

Deep Brain Stimulation (DBS) is a novel, highly effective therapy which has revolutionized the management of a number of neurologic movement disorders. The therapy involves implantation of small electrodes in deep brain structures connected to a pulse generator, which is so bulky that it should to be implanted in the upper chest wall and wired subcutaneously to the electrode contacts emerging from the top of the head. According to several studies the subcutaneous extension wires and their connectors are a source of morbidity for patients and the primary cause of mechanical failure in DBS implants.

The main objective of this research is to develop a significantly smaller, more efficient, integrated microstimulator that can be practically attached to the head at the point of electrode entry to the brain. Existing DBS circuits, inherited from pre-existing cardiac pacing technology, only generate square-shaped pulses and can only control the pulse width, frequency, and either voltage or current amplitude. *Voltage-controlled stimulation* (VCS) provides greater power-efficiency but it can only be used when the electrode and tissue impedances are well known. *Current-controlled stimulation* (CCS) is safer and provides more control over the stimulus parameters, but it consumes more power. Today's DBS implants are VCS-based and manufacturers have to indicate the safety limits by providing curves and data tables in terms of the electrode/tissue impedance, pulse width, and pulse amplitude.

We have designed novel switched-capacitor based stimulation (SCS) circuitry that directly controls the amount of injected charge into the neural tissue. This is accomplished by generating charge-controlled, exponentially decaying bursts of stimulus pulses. The SCS circuit combines the power efficiency of the VCS circuits with the safety and stimulation parameter controllability of the CCS circuits. This innovative circuitry and technique is expected to substantially simplify the pulse generator architecture and reduce its size and power requirements relative to the existing DBS hardware.

In the next phase of this project we will evaluate and compare the efficacy and efficiency of three deep brain stimulation techniques using VCS, CCS, and SCS circuits. Our methodology will be to apply various stimulation waveforms using each of the three circuits and evaluate the results in terms of neurophysiologic response and required battery power. To accomplish this comparison we will combine circuit simulations and excitable neural tissue models. Also, prototype computer-controlled VCS, CCS, and SCS pulse generators will be fabricated and used in short-term *in vitro* rat brain slice experimental preparation and neurophysiological activity measuring techniques to validate the results of computer simulations. If successful, a integrated miniature version of the SCS microstimulator will be fabricated and tested in long-term in vivo experiments on rat or primates.

This work is supported by Interdisciplinary Faculty Research and Professional Development Program, Division of Research Administration, NC State University.

An Inductively Powered Multichannel Wireless Implantable Neural Recording System

Ming Yin and Maysam Ghovanloo

Department of Electrical and Computer Engineering, North Carolina State University, Raleigh, NC

Wireless recording of the neural signals from a large number of recording sites is highly desired because a growing number of neuroscientists have become interested in visualizing the extracellular activities of thousands of single neurons in awake, freely moving animals. High site-count neural recording systems are currently hard-wired, and the tethering effects of the wires interfere with natural animal behavior and bias the overall results. So far, most of the reported wireless neural recording systems have been battery powered, and therefore, not fully implantable except for a short period of time. The objective of the present research is to develop an inductively powered 15-channel wireless implantable neural recording (WINeR) system for long-term *in vivo* experiments.

The system can record from either microwire electrodes or micromachined arrays. For every recording channel, a low-noise, low-power amplifier (LNA), which is capable of amplifying signals from milliHertz to kiloHertz range, is used to amplify the acquired neural signals. A capacitive high-pass filter at the input of every LNA rejects the large DC offset generated at the electrode-tissue interface, but not low-frequency evoked potentials that may contain significant physiologic information. Fifteen identical neural recording channels, plus a constant reference voltage (MARK) that marks the beginning of each frame, are time-division multiplexed (TDM) by a 16 to 1 multiplexer that is controlled by a 4-bit counter. A sample and hold (S&H) circuit follows the TDM to stabilize the acquired samples before pulse-width modulation (PWM). The PWM is dedicated to convert the analog signal at the output of the S&H to a pseudo-digital signal that is more robust against noise.

A voltage-controlled oscillator (VCO) converts the PWM signal to a frequency shift keyed (FSK) carrier in the industrial, scientific, and medical (ISM) band. Due to the short-range application of the WINeR system (within the animal cage), the VCO output can be directly applied to a miniature patch antenna. A commercial ISM-band receiver will be used as the external part of the system. The received PWM signal will be directly converted to digitized samples using a high-frequency counter on a PC data acquisition card. Finally, by demultiplexing the TDM samples, the original neural signals are reconstructed. The WINeR implant also contains a receiver coil followed by an on-chip rectifier, filter, and regulator that provide the rest of the implant with a clean DC supply. The power carrier frequency is selected to have minimum interference with the neural signals and ISM carrier. The WINeR system has been implemented in the AMI 0.5-µm process and submitted for fabrication.

This work is supported by startup funds provided by the Department of Electrical and Computer Engineering, North Carolina State University.

Kinetics of Interfacial Electron Transfer Reactions at the Vitreous Humor-Retinal Prosthesis Electrode Interface

Charlene A. Sanders[1], Evan J. Nagler[1], David Zhou[2,¶], J. D. Weiland[3], M. S. Humayun[3], and Elias Greenbaum[1]

[1]Oak Ridge National Laboratory, Oak Ridge, TN
[2]Second Sight, LLC, Sylmar, CA
[3]Doheny Eye Institute/University of Southern California Keck School of Medicine, Los Angeles, CA

Photosensitive multipixel microelectrode arrays that are implanted on the retina can stimulate viable retinal neuronal cells and restore partial vision in patients suffering from degenerative macular disease and retinitis pigmentosa. Criteria for electrode performance include the safe and effective depolarization of retinal neurons at charge densities in the range 0.1-1.0 mC/cm^2 and relatively low resistance to current flow. Safe stimulation in physiological solution implies no tissue damage and long-term, stable electrode function without degradation or formation of local byproducts of electrochemical reactions. Stimulation pulse patterns that fit these criteria are balanced, biphasic, and can have an intraphase delay. Under the right conditions, surface electrochemistry that occurs during the cathodic phase is reversed during the anodic phase. Using original experimental instrumentation, we report real-time kinetic measurements on the upper limits for current amplitude and dwell time at the platinum-vitreous humor interface for hydrogen formation during the cathodic wave of 60 Hz biphasic electrode pulse stimulation. We present data for a platinum electrode of 150 μm diameter that was sealed in borosilicate glass tubing and cut and polished perpendicular to the long dimension of the wire. Using a tin-oxide hydrogen sensor, we report thresholds for the onset of hydrogen formation as a function of charge density per pulse. Images (SEM) of the electrodes taken before and after stimulation will be presented.

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[¶]Brandeis University student participant in the Science Undergraduate Laboratory Internship program, Oak Ridge Institute for Research and Education.

An Open- and Closed-Loop Control System for Generating Over-Ground Locomotion Using Functional Electrical Stimulation

L. Guevremont, J.A. Norton, B. Lau, and V.K. Mushahwar

Biomedical Engineering, University of Alberta, Edmonton, Alberta

Topic area: Models and Stimulation Paradigms

Currently available functional electrical stimulation (FES) systems for restoring locomotion after spinal cord injury (SCI) have limited clinical success, partially due to the use of controllers that generate unnatural gait patterns, often owing to the use of patient-triggered buttons to initiate each step. The goal of this study is to develop a closed-loop controller that generates appropriate phase transitions without the need for patient intervention. In a previous study, simple open- and closed-loop controllers were used to trigger intraspinal microstimulation (ISMS) and evoke reciprocal extension and flexion movements. This resulted in the generation of in-place stepping in cats with SCI[1]. In the current study, we extend the design of the controller to generate functional over-ground stepping using a four-phase gait cycle. We also developed a 16-channel stimulator (1 uA-10 mA) that allows independent modulation of each stimulation channel and will permit us to test the control system using multiple FES techniques, including ISMS and intramuscular (IM) stimulation. The closed-loop controller uses information about the current state of the limbs to initiate phase transitions in a manner similar to subconsciously controlled, able-bodied locomotion. Established *if-then* rules governing stance-to-swing[2] and swing-to-stance transitions[3] are implemented using hip angle (tilt sensor) and ground reaction force (force plate) signals.

If-then rules: stance-to-swing transitions
IF ipsilateral hip extended
AND ipsilateral limb unloaded
AND contralateral limb loaded
THEN initiate flexion in ipsilateral limb

If-then rules: swing-to-stance transitions
IF ipsilateral hip flexed
THEN initiate extension in ipsilateral limb

These rules enable us to decouple the legs and allow for a period of double limb support. Protraction (terminal swing) and retraction (terminal stance) phases are implemented in order to provide the forward reach and backward propulsive force required for over-ground locomotion. We tested the controller and found that phase transitions can be successfully triggered by using simple threshold crossing algorithms applied to the tilt sensor and force plate signals. Robust phase switching was seen when threshold values of approximately 20% of the maximum sensor signal swing were used to define the state of the system (i.e., hip extension vs. flexion). Work is currently underway to test the robustness of the controller during stimulus-driven locomotion. Spinalised cats with ISMS and IM implants will be used to show that robust overground locomotion can be generated using simple *if-then* rules.

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Reversible Transmission Block of the Feline Pudendal Nerve via High Frequency Alternating Current Stimulation

Kenneth J. Gustafson 1,2, Narendra Bhadra 1, Niloy Bhadra 1, and Kevin Kilgore 3

Department of Biomedical Engineering, Case Western Reserve University, Cleveland, OH
2 Louis Stokes Cleveland Department of Veterans Affairs Medical Center, Cleveland, OH
3 MetroHealth Medical Center, Cleveland, OH

Reversible nerve block of the pudendal nerve would provide a valuable tool for restoring bladder function for individuals with bladder sphincter dyssynergia. Reversible nerve block with high frequency alternating current stimulation (HFACS) has been recently demonstrated in frogs and rats. The objective of this study was to evaluate the effectiveness of HFACS to produce pudendal nerve block and reduce external urethral sphincter pressure.

The bladder was emptied, catheterized and isolated in six adult male cats under alpha-chloralose anesthesia. External urethral sphincter (EUS) pressures were recorded with a micro-transducer catheter positioned at the external sphincter. A bipolar electrode was placed proximally on the pudendal nerve and urethral sphincter efferent fibers stimulated (twitches 1 Hz; tetanic 33 Hz) with constant current stimuli (100μs, supramaximal). A tripolar nerve cuff electrode (blocking electrode) was placed on the deep perineal or pudendal nerve which contain efferent fibers to the EUS. The distal tripolar electrode was connected to a waveform generator to deliver sinusoidal HFACS (1 to 30 kHz, 1-10 V_{p-p}). For each trial, supramaximal proximal stimulation was applied through the duration of the run to evoke EUS twitches. Five seconds after the onset of proximal stimulation, the blocking HFACS was applied for 10 to 30 seconds. Proximal stimulation was continued for at least 5 seconds after blocking stimulation.

HFACS completely and reversibly blocked the evoked sphincter response in all cats. Complete HFACS induced block of evoked sphincter twitch and tetanic contractions were observed at frequencies between 1 and 30 kHz and amplitudes between 4 and 10 volts. The threshold voltage for complete transmission block increased with frequency. During evoked twitch runs, HFACS evoked an initial spike in EUS pressure before the onset of complete block. Evoked EUS pressures were reduced by >95% during HFACS and in most cases immediately returned to initial levels once HFACS ended. Stimulation of the deep perineal nerve distal to the blocking electrode during HFACS produced EUS contractions, excluding muscle fatigue as a causal factor and verifying the local nature of the block.

High frequency pudendal nerve stimulation can reversibly block EUS contractions. Reversible HFACS block may provide a valuable tool to block EUS activity and produce voiding in individuals with bladder sphincter dyssynergia.

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A Comparative Analysis of Fundamental Nerve Fascicular Anatomy: Physiologic Limits and Implications for Nerve Cuff Electrode Design

Kenneth J. Gustafson[1,2] and Evan K. Artis[1]

[1]Department of Biomedical Engineering, Case Western Reserve University, Cleveland, OH
[2]Louis Stokes Cleveland Department of Veterans Affairs Medical Center, Cleveland, OH

Distal nerve branches may be oriented as groups of fascicles within a proximal peripheral nerve trunk. Individual fascicles or groups of fascicles can be selectively stimulated with multi-contact nerve cuff electrodes. Selective stimulation of individual fascicles can provide control of multiple muscles or organs with a single implant. The ability to selectively stimulate a nerve is strongly dependent on fascicular anatomy; however, knowledge of fascicular organization across species and nerves is limited. The design of cuff electrodes for clinical applications based on preclinical animal models may be dependent on differences in fascicular anatomy. The objective of this study was to perform a comparative analysis of the physiologic ranges of fascicular sizes and frequencies across a range of species and peripheral nerves.

Over 50 specimens from femoral, sciatic, pudendal, and hypoglossal nerves in rats, cats, dogs, humans and a calf were obtained at proximal potential anatomical locations for device implantation. These samples were histologically processed and nerve and fascicular anatomy (area, major and minor diameters, eccentricity, and frequency) were quantified using customized software.

In contrast to current dogma, our data demonstrates that as total fascicular area increases with body mass, the number of fascicles within a nerve increases rather than the size of the fascicles. Across species and nerves, 95% of fascicles were less than 600 _m in diameter. As total fascicular area increased with mass, the ratio of nerve width to height increased, demonstrating that nerves become flatter with increased mass.

These data suggest that there exists a physiologic upper limit to fascicular diameter independent of body mass or nerve size. This fundamental anatomical property may simplify the development of computer and animal models for individual clinical applications. The relatively flat cross-section of human specimens demonstrates that nerves are flat *in situ* and suggests that flatter electrode designs such as the Flat Interfacing Nerve Electrode (FINE) may be more appropriate for human applications. These results provide the basic design constraints for the design of nerve cuff electrodes for novel human applications based on fundamental neural anatomy and engineering principles, and may assist the translation of preclinical studies to clinical applications.

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Quantification of Human Sciatic Nerve Anatomy:
Implications for Neural Prostheses Utilizing Nerve Cuff Electrodes

Kenneth J. Gustafson[1,2], Yanina Grinberg[1], Matthew Stone[1], and Ronald J. Triolo[1,2,3]

[1]Department of Biomedical Engineering, Case Western Reserve University, Cleveland, OH
[2]Louis Stokes Cleveland Department of Veterans Affairs Medical Center, Cleveland, OH
[3]Department of Orthopedics, Case Western Reserve University, Cleveland, OH

The next generation of neural prostheses utilizing nerve cuff electrodes to restore standing in individuals with spinal cord injury (SCI) and to prevent footdrop or provide active propulsion after hemiplegia require detailed knowledge of lower sciatic nerve neuroanatomy. The objectives of this study were to quantify the fascicular anatomy and morphology of the human lower sciatic nerve, and evaluate the potential of selective activation of ankle musculature with a multicontact nerve cuff electrode.

Four complete sciatic nerves and all distal branches were dissected from the piriformis to each muscle entry point to characterize their branching patterns and diameters. Fascicle maps were created for three samples from serial sections from each distal terminus below the knee through the junction of the tibial and common fibular nerves above the knee.

Consistent branching patterns were observed between specimens. Distal nerves were represented as individual fascicles or distinct fascicular areas in proximal nerve sections; however, fascicular plexusing in one sample limited the ability to trace individual fascicles proximally past the branching point of the tibial and common fibular nerves. Isolated functional grouping of fascicles from plantar flexors and dorsiflexors were more readily identified in the tibial and common fibular nerves than the sciatic nerve. Branch-free lengths of the distal sciatic, tibial, and common fibular nerves from the bifurcation to the first branch were 5.1 ± 1.5 cm (range 3.7-6.7 cm), 7.0 ± 0.4 cm (range 6.5-7.2 cm), and 5.0 ± 2.2 cm (range 2.7-7.0 cm), respectively.

The lower sciatic nerve fascicular anatomy and morphology are conducive to selective activation of dorsiflexion and plantar flexion with cuff electrode(s) on the lower sciatic nerve, which may improve current systems for walking after hemiplegia as well as the next generation of standing and walking systems for SCI.

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Long-Term Performances of Implanted Microelectrode Arrays With Multiple Electrode Designs

M. Han, D.B. McCreery, L.A. Bullara, and X. Liu

Neural Engineering Program, Huntington Medical Research Institutes, Pasadena, CA

Topic area: Electrodes

Many applications in neural prosthesis and brain-machine interfaces today utilize electrical stimulation and recording using chronic microelectrode arrays. Our aim in this study is to determine a suitable set of dimensions for penetrating electrodes by investigating and comparing the long-term performances of multiple electrode designs in each array. We present preliminary results from ongoing electrochemical characterization and monitoring of two microelectrode arrays.

The activated iridium oxide electrodes were fabricated from iridium wires and were insulated with Parylene C, except for the tips. The two arrays, each with 16 of these electrodes, were implanted into the lateral part of the postcruciate gyrus of two cats. Each array contained eight electrodes with "sharp" tips (radius of curvature approximately 3 μm), and eight with "blunt" tips (radius of curvature of approximately 5 μm). In each group of the eight electrodes, four had exposed-geometric surface areas of approximately 2,000 μm^2 and four had surface areas of approximately 4,000 μm^2. Characterization parameters included AC impedance, charge storage capacity from cyclic voltammetry, and voltage transients during current pulsing, as well as the amplitudes of spontaneous action potentials ("spikes") from cortical neurons. These measurements were taken from pre-implantation to every 2 weeks thereafter.

In electrochemical measurements *in vitro*, as expected, there was strong inverse correlation between electrode tip areas and impedances, and positive correlation between electrode tip areas and charge storage capacities. In the subsequent measurements *in vivo* through week 16, some changes in impedances and charge storage capacities were observed. However, changes in the impedances were smaller and have largely maintained their relation to electrode tip areas. At the start of week 16, spontaneous extracellularly recorded action potentials consistently exhibited signal-to-noise ratios of greater than 4:1 on most of the electrodes. To date, the different sets of electrodes have retained their recording and stimulation capabilities, even as their electrochemical characteristics have changed somewhat.

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In Vivo *Studies of Nanoscale Laminin Coated Neural Probes*

Wei He, George C. McConnell, and Ravi V. Bellamkonda

Neurological Biomaterials and Therapeutics, WHC Department of Biomedical Engineering, Georgia Institute of Technology/Emory University, Atlanta, GA

A stable interface between silicon microelectrode arrays (Si-MEAs) and brain tissue is critical for achieving chronic *in vivo* recording of neural activity. However, such stability is usually compromised by scar tissue formation and subsequent fibrotic encapsulation at the site of implantation. We previously reported the development and *in vitro* testing of a nanoscale laminin (LN) coating on Si/SiO_2 surfaces using electrostatic layer-by-layer (LbL) self-assembly. We had demonstrated that neural cell attachment and differentiation was most markedly increased by multilayers of polyethyleneimine (PEI) and LN. In this study, we investigate the cortical response to the nanoscale LN coatings *in vivo*. Both coated and uncoated acute Michigan probes were implanted in the rat cortex. Cellular and tissue responses were assessed 1 day, 1 week, and 4 weeks after implantation using quantitative immunohistochemistry. Cortical tissues were immunostained for GFAP (astrocytes), ED-1 (microglia/macrophage), and NeuN (neurons). Compared to the uncoated bare Si probe, a significant decrease in immunoreactivity of GFAP and ED-1 was observed around the coated probe after 4 weeks. Additionally, the nanoscale LN coatings did not adversely affect the electrical properties of the probes as evaluated by impedance spectroscopy and acute recording in the rat cortex. To determine the mechanism by which LN coatings reduce chronic inflammation *in vivo*, we conducted real-time PCR studies using primary microglia cultured on the LN surface *in vitro*. Interestingly, we observed a significant *upregulation* of pro-inflammatory cytokines, TNF-α, IL-1, and IL-6 mRNA, in microglia on LN-substrates compared to non LN-substrates. These results indicate that LN coatings may, counterintuitively, stimulate microglia immediately after implantation, enhancing their ability to clean up the debris after injury, and aid the intrinsic repair mechanisms of CNS for limiting the wound site, preserving tissue in the immediate vicinity of the injury, and assisting in minimizing secondary injury/inhibition.

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Hydrogel-Conductive Polymer Electrodes for Communication Through the Glial Scar

Jeffrey L. Hendricks[1], Sarah Richardson-Burns[2], and David C. Martin[1,2,3]

[1]Department of Biomedical Engineering, University of Michigan, Ann Arbor, MI
[2]Department of Materials Science & Engineering, University of Michigan, Ann Arbor, MI
[3]Department of Macromolecular Science & Engineering, University of Michigan, Ann Arbor, MI

Topic area: Materials and Devices

Neural prosthetic devices implanted in the brain and central nervous system consistently experience insulating scarring and fibrous encapsulation, which limits signal transduction and stability. Strategies to reduce the extent of glial scarring and to overcome its insulative effects include antifouling coatings, local anti-inflammatory drug release, transfected cell delivery, and softer probe substrates, such as parylene. Since any biomedical device implanted into the body will experience some degree of fibrous encapsulation, it is important to consider strategies for communicating with neurons despite glial scarring. Conductive polymers offer the ability to deposit molecularly thin electrode tendrils through hydrogel matrices. The resulting highly diffuse polymer network extends the electrodes' surface closer to the viable neurons while the hydrogel scaffold limits protein adsorption to the electrode and creates a permissive environment for cell immobilization.

Hydrogels were formed from 1% alginate powder in phosphate-buffered saline. Murine primary cortical cultures were harvested from E18 mice and dissociated manually and mixed with the alginate solution. Gelation occurred with the addition of the divalent cation Ca^{2+}. Neural cell-containing alginate hydrogels were cultured in Neurobasal media supplemented with B-27 and kept in a humidified incubator at 37˚C. The conductive polymer, poly(ethylene dioxythiophene) (PEDOT), was deposited electrochemically from a monomeric solution of ethylene dioxythiophene (EDOT) in PBS under galvanostatic conditions. PEDOT can be deposited into the hydrogel matrices containing nerve cells to produce living hydrogel polymer electrodes.

The hydrogel-conductive polymer electrodes were used to electrically stimulate nerve cells immobilized in the matrix. Visualization of synaptic vesicle activity with FM1-43 demonstrates that the electrodes are capable of stimulating nerve cells through the conductive polymer coatings. The electrical behavior of these electrodes was characterized by Electrochemical Impedance Spectroscopy (EIS) and by Cyclic Voltammetry (CV) and compared to existing planar microfabricated electrodes. The morphology of the hydrogel-conductive polymer electrode complex was analyzed by visual and electron microscopy to determine the integration of conductive polymer into the porous scaffold.

In order to fully control the morphology of nerve cells contained within the hydrogel-conductive polymer electrodes, it is necessary to incorporate extracellular matrix components into hydrogel. Future studies will include the use of functionalized hydrogels to induce neurite outgrowth within the hydrogel-conductive polymer electrode.

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EMG-Based Control for Upper Extremity Neuroprosthesis

Juan Gabriel Hincapie, Dimitra Blana, Edward K.J. Chadwick, and Robert F. Kirsch

Department of Biomedical Engineering, Case Western Reserve University,
Cleveland Functional Electrical Stimulation Center, Cleveland, OH

Topic areas: Models and Stimulation Paradigms; Neural Prosthesis; Sensory/Motor and Functional Neural Stimulation

The goal of this project is to enhance the benefits of functional electrical stimulation (FES) for individuals with cervical mid-level spinal cord injury (C5-C6 SCI) by providing upper arm function that complements the current hand function provided by FES systems. As a result of stimulation to these shoulder and elbow muscles, individuals will be able to increase their range of motion providing overhead and across reaching, improve their ability to assist during transfers and perform posture changes, reduce their shoulder pain by improving scapular instability, and, in general, provide more natural and effortless way of controlling the movement of their arms. A controller that extracts information from recorded EMG activity of muscles under retained voluntary control and processes these signals to generate the appropriate stimulation levels for paralyzed muscles was designed using a dynamic musculoskeletal model of the arm. Different arm movements were recorded from able-bodied subjects and these kinematics served as input to the model. The model was modified to reflect C5/C6 SCI, and inverse simulations were run to provide muscle-activation patterns corresponding to the movements recorded. One set of "voluntary" muscles and one set of "stimulated paralyzed" muscles were selected as input and output to the controller, based on each muscle's relevance as suggested by the simulations. A neural network controller was trained to predict "stimulated paralyzed" muscle activations using "voluntary" muscle activations as inputs. The neural network controller was able to predict the activation level of three paralyzed muscles with less than 2% error, using four voluntary muscles as inputs.

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Cortical Prosthesis: Proof-of-Concept in Hippocampus Slice

Min-Chi Hsiao[1], Vijay Srinivasan[3], Gopal Erinjippurath[2], Ashish Ahuja[2], Ghassan Gholmieh[1], Spiros H. Courellis[1], Dong Song[1], Jeff LaCoss[3], Jack Wills[3], Armand R. Tanguay, Jr.[2,4], Vasilis Z. Marmarelis[1], John J. Granacki[2,3], and Theodore W. Berger[1,4]

[1]Department of Biomedical Engineering, University of Southern California, Los Angeles, CA
[2]Department of Electronic Engineering, University of Southern California, Los Angeles, CA
[3]Information Sciences Institute, University of Southern California, Los Angeles, CA
[4]Neuroscience Program, University of Southern California, Los Angeles, CA

We have proposed a biomimetic electronic device to replace a damaged CA3 (CA = cornu ammonis) subregion of the hippocampal slice. The hippocampus is a cortical structure that has been associated with learning and memory. It is thought to be involved in the formation of new memories and the consolidation of short-term memories. The major intrinsic circuitry of the hippocampus consists of an excitatory cascade of Dentate Gyrus (DG), CA3, and CA1 subregions, and is maintained in a transverse slice preparation. The input signals from perforant-path (PP) fibers excite the DG granule cells. The DG output is sent to CA3 pyramidal cells through the mossy fibers. Then, the Schaffer collaterals transmit the processed signal from the CA3 region to CA1 pyramidal cells.

The prosthetic demonstration consists of four parts. First, build an artificial CA3: within the intact slice, we apply 1,200 random-impulse trains (RITs) to PP and use a multielectrode array (MEA, www.mutilchannelsystems.com) system to record the trisynaptic responses in DG, CA3, and CA1. We analyzed the amplitude and calculated the nonlinear relationship between DG and CA3, then developed the CA3 computational model and implanted into FPGA (field-programmable gate array) device. Second, create a CA3-damaged preparation: use the wire/rubber-made cutter, surgically eliminating the CA3 to CA1 connection by transecting the Schaffer collaterals; the effect of transection and activity in CA1 should be confirmed. Third, apply the same RITs and connect the DG output to the FPGA; the corresponding estimated CA3 output can be calculated, then sent back to CA1 subregion. Fourth, data evaluation: compare the CA1 EPSPs in the intact slice with the CA3-damaged slice replaced by the FPGA device.

Our results show very good agreement between data from intact slices and transected slices with the hardware-substituted CA3. The average NMSE (normalized mean square error) was less than 10%. Thus, propagation of temporal patterns of activity from DG_FPGA_CA1 reproduces that observed experimentally in the biological DG_CA3_CA1 circuit.

PECVD a-SiC:H and Parylene Encapsulation for Chronically Implanted Neural Recording Devices

Jui-Mei Hsu[1], Loren Rieth[1,2], Sascha Kammer[3], Klaus Peter Koch[3], Richard A. Normann[4], and Florian Solzbacher[1,2,4]

[1]Department of Material Science and Engineering, University of Utah, Salt Lake City, UT
[2]Department of Electrical Engineering, University of Utah, Salt Lake City, UT
[3]Department Medical Technology and Neuroprosthetics, Fraunhofer Institute for Biomedical Engineering, Germany
[4]Department of Bioengineering, University of Utah, Salt Lake City, UT

Topic area: Materials and Devices

A fully integrated, wireless neural recording device is being developed to free patients from the restriction and risk of infection associated with a wired connection. This device requires a stable, biocompatible encapsulation layer at the interface between the recording device and the brain neural tissue to maintain the long-term recording characteristic of the device. Amorphous silicon carbide (a-SiC:H) was investigated for the first time as an insulating, hermetic, and biocompatible encapsulation for this device. We focused on a low temperature deposition process to avoid degrading the integrated device during the encapsulation process. The a-SiC:H films were compared with the well-known biocompatible encapsulation material, Parylene.

A plasma-enhanced chemical vapor deposition (PECVD) system was used to deposit the a-SiC:H layers. The deposition conditions included a pressure range from 200 mTorr to 800 mTorr and a substrate temperature range from 150 ˚C to 300 ˚C. The film properties were evaluated by ellipsometry, energy dispersive X-ray analysis (EDX), and Fourier transform infrared spectroscopy (FT-IR) to investigate the refractive index, atomic composition, and chemical bonding in the film, respectively. Contact angle measurements found that the a-SiC:H layers are often slightly hydrophilic.

AC (impedance spectroscopy) and DC electrical measurements were used to evaluate film degradation, delamination, and dissolution. One-um thick a-SiC:H and Parylene thin films were deposited on oxidized silicon and quartz substrates containing Ti/Pt (50 nm/330 nm) interdigitated electrodes (IDE). These test chips were placed in Ringer's solution at 37 °C for impedance spectroscopy tests. Material degradation, adhesion failure, property changes, and electrical short circuits in the interface between the encapsulation and substrate change the impedance. Preliminary data demonstrate that this technique will be a useful tool to investigate the encapsulation performance. Parylene was also investigated by leakage current (DC) tests, and these results will be compared with impedance spectroscopy data. The IDE test structures were coated with 20 µm of Parylene and immersed in a 0.9% NaCl solution. The leakage current was measured for 5 months with a 5 V bias at 37 °C and measured less than one nA of current. Preliminary dissolution rates for a-SiC:H were measured using a 90 ˚C PBS buffer.

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2005 Progress on a Direct Brain Interface Based on Detection of ERPs in ECoG

J.E. Huggins, S.P. Levine, V. Solo, J.A. Fessler, D.M. Minecan, S.Y. Chun, R.C. Welsh, R.K. Kushwaha, and S.L. BeMent

University of Michigan, Ann Arbor, MI

Topic: Brain Computer/Machine Interface

The University of Michigan Direct Brain Interface project seeks to detect voluntarily produced event-related activity in human electrocorticogram (ECoG) during actual or imagined movements to operate assistive technologies. The project includes functional magnetic resonance imaging studies (Swaminathan et al., 2004), off-line data analysis, and feedback experiments.

Subjects from an epilepsy surgery program have subdural electrodes implanted for clinical purposes. They perform self-paced movements while electromyogram (EMG) onset is recorded to partially label rest and event classes. Our previous cross-correlation template matching (CCTM) method implicitly used a white noise model that ignores event-related power spectrum changes. A tractable model that includes spectral changes was made by assuming that every data point belongs to one of two classes (resting/event); each class has a zero mean Gaussian distribution with different and constant covariances, allowing simple hypothesis testing by the Neyman-Pearson lemma. For simplicity, we ignored the ERP component. An autoregressive (AR) model is used for each covariance.

The likelihood ratio simplifies (to within irrelevant constants) to the quadratic form:

$$\Lambda(x) = x' \, (K_0^{-1} - K_1^{-1}) \, x. \qquad (1)$$

For real-time implementation, the AR model reduces inversion of large covariance matrices to simple finite-impulse response (FIR) filters, with the running mean of the difference between the squared filter outputs used as the test statistic.

Applying this QUAD method to self-paced, partially labeled ECoG presents challenges. The time of EMG onset is labeled, but the time the subject decided to move is not. We label as $H1$ everything within a window size w and a center location c relative to EMG onset (values selected with maximum likelihood estimation). The remaining data, excluding a transition zone, is labeled as $H0$. A hysteresis threshold provides a data-dependent lockout and reduces multiple detections of a single event.

QUAD detection produced a hit percentage above 90% and a false positive percentage below 10% for 17 of 233 channels compared to only 1 for CCTM while reducing detection delay. With CCTM feedback, one subject used imagined tongue movements on line with 82% hits and 16.3% false positives. Replacing the CCTM method with the QUAD in feedback experiments should improve interface accuracy and response time.

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Reduction of Aspiration Through Stimulation of the Recurrent Laryngeal Nerve: Development of a Second-Generation System

Jeffrey C. Huynh[1], Nina S. Zobenica[1], Michael Broniatowski[2], and Dustin J. Tyler[1,3]

[1]Department of Biomedical Engineering, Case Western Reserve University, Cleveland, OH
[2]St. Vincent's Charity Hospital, Cleveland, OH
[3]Cleveland VA Medical Center, Cleveland, OH

Topic area: Sensory/Motor and Functional Neural Stimulation

Aspiration is defined as the entry of foreign matter into the airway and lungs. A common consequence of dysphagia (difficulty in swallowing), aspiration-pneumonia following stroke is directly related to an estimated 40,000 deaths each year in the United States. Currently, clinical trials are being conducted to evaluate the efficacy of aspiration reduction by means of stimulation of the recurrent laryngeal nerve (RLN), a nerve known to cause adduction of the vocal folds. This present system utilizes a single-channel stimulator, which requires appropriate coupling of the external transmitter to an internal stimulating electrode, provides an unknown current as it is dependent on the coupling and stimulating load, and requires patient initiation of stimulation. A second-generation system, still utilizing whole stimulation of the RLN, is being developed and tested in a dog model. Quantitative analysis of the effects of RLN stimulation will be conducted by evaluating intrinsic larynx muscle recruitment and vocal fold closure pressure.

Intrinsic larynx muscle recruitment and order of recruitment will be evaluated using bipolar EMG electrodes with percutaneous leads. A single-sensor, solid-state pressure transducer introduced in between the vocal folds will be used to evaluate pressure. Stimulation of the RLN is provided by a BION single-channel stimulator.

Developed by the Alfred Mann Foundation, this single-channel stimulator provides a smaller implant, fine control over current-stimulus generation, and current-controlled output. Two methods of stimulation will be evaluated: placing the stimulator next to the nerve for gross stimulation of the nerve and surrounding tissue, and a leaded electrode using a Huntington Medical Research Institute nerve-cuff electrode that wraps around the nerve.

The experimental system design has been completed, and equipment for stimulation, data acquisition, and patient monitoring has been purchased. Currently, the system is being built, tested, and calibrated. We scheduled the first dog implant for early July.

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Hybrid Cellular-Silicon Engineered Devices for Neural Prosthetics

Jenna L. Rickus[1,2,3] and Pedro Irazoqui[2]

[1]Department of Agricultural and Biological Engineering, Purdue University, West Lafayette, IN
[2]Weldon School of Biomedical Engineering, Purdue University, West Lafayette, IN
[3]Bindley Bioscience Center, Purdue University, West Lafayette, IN

The 2002 NIH workshop on Models for Epilepsy and Epileptogenesis reported that current treatment options are not sufficient, the rate of development of new treatment strategies is slowing, and new approaches to treatment discovery and evaluation are essential (Stables et al., 2002). Two major problems facing current epilepsy treatments are drug resistance and unwanted side effects. Despite a growing number of antiepileptic drugs, roughly 30% of patients remain pharmacoresistant (Leppik, 1992). While the specific mechanisms of resistance remain unclear, they likely include the poor spatial targeting of the drug to specific brain regions, and tolerance development through cellular and molecular adaptation over time. Poor or improper spatial targeting is also a significant cause of unwanted side effects (Sills et al., 2003). Spatial and temporal targeting of drug action to specific brain regions immediately prior to and during seizure would represent a significant advancement in the ability to treat epilepsy without side effects. Similar arguments apply to current efforts to treat Parkinson's disease (Nutt et al., 2001) and suppress pain in opioid-tolerant patients (Sun et al., 2004), among others.

Most of today's therapeutic interventions modulate neurotransmitter levels as a static step change, with wide spatial effects and modulation on the timescale of hours, yet neurotransmitter signaling is dynamic, spatially restricted, and modulated on a timescale of milliseconds. For closed-loop chemical devices involving mechanical and electrical drug pumps, the problem of a long-term drug source or reservoir has not been solved. The transplantation of engineered neurotransmitter-releasing cells is a more biological approach. In essence, the cells serve as the drug factory and pump, producing and releasing the lacking neurotransmitter. However, with no specific control mechanism to respond to seizure triggers, resistance to continuous release from transplanted cells will continue to be a problem. We are developing a cell-based therapy with closed-loop control to provide neurotransmitter release from a renewable engineered-cell source. This therapy is being engineered as a hybrid cellular-silicon neural implant device. Such a neuroengineered device is now feasible, considering the recent and rapid advances in neural implants (Irazoqui et al., 2003), brain machine interfaces (Nicolelis, 2003), and cell-device integration (Otto et al., 2004).

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Interconnects and Packaging for Microactuated Microprobes

Nathan Jackson and Jit Muthuswamy

Harrington Department of Bioengineering, Arizona State University, Tempe, AZ

Topic area: Neural Prosthesis

Packaging and interconnects have a significant role in determining how long a device remains functional after it is implanted. It is often desirable that the packaged device be as light and small as possible. However, interconnects and packaging of implantable MEMS devices poses a greater challenge, due to the presence of moving parts. We report here a novel packaging and interconnect strategy for our microactuated microprobe chip using flip-chip techniques.

We use flip-chip on flex (FCOF) techniques instead of traditional flip-chip approaches to optimize the packaging and interconnection. Gold-stud bumps were placed on bond pads, which were used for actuating the individual electrodes and for recording neural activity. The gold-stud bumps were made using standard wire-bonding techniques and were approximately 75 μm high. The flex circuits were made using polyimide substrates with gold-bond pads that were on the order of 100 μm^2 and traces that were 25-μm wide. Standard photolithography techniques were used to pattern the designs onto the polyimide substrates. The flex circuit was bonded to the stud bumps on the microactuated microprobe chip using thermo-compression or thermo-sonic bonding. Since gold-gold connections were made, there was no need for an underfill.

The packaging reliability for the microactuators was also assessed under different conditions. The device was placed under high humidity conditions and tested for functionality. Further thermal cycling, thermal shock, and tensile strength tests will be needed to rigorously test the reliability of the packaging under extreme conditions.

The old method of packaging was to place the chip on a chip-carrier and wire bond to the chip carrier. By using FCOF techniques, interconnects and packaging of the chip were reduced to the size of the chip, which corresponds to a reduction of size from 951 mm^3 to 19 mm^3. The weight of the device was also reduced by one order of magnitude from approximately 8 g to 150 mg. Accelerated humidity testing on the microactuators was done under 99% relative humidity, and this revealed an estimated life time of 2.2 years under 99% relative humidity at 37^oC.

This shows that the FCOF technique using gold-to-gold connections is a viable approach for successful interconnects and packaging in implantable MEMS devices.

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Plasticity of Preferred Directions in Motor Cortex

B. Jarosiewicz, M. Velliste, and A.B. Schwartz

Department of Neurobiology and the Center for the Neural Basis of Cognition, University of Pittsburgh, Pittsburgh, PA

Topic area: Neural Prosthesis

The finding that individual neurons "encode" various facets of the world was fundamental to our early understanding of brain function. The more recent finding, that neural coding is *plastic*, is a fundamental principle of nearly equal magnitude. Many studies have shown compellingly that neurons can change what they encode in association with learning; however, it has been very difficult to establish a causal link between the observed changes in neural activity and the behavioral manifestation of learning. This problem can be overcome by taking advantage of the "brain control" paradigm used in the development of neural prosthetics, in which the causal link between neural activity and its effects on the external world is defined, and therefore can be changed, by the experimenter.

Rhesus monkeys performed a 3D center-out task in virtual reality under brain control, in which the spiking activity from a simultaneously recorded ensemble of motor cortical cells was converted to cursor movement using our previously described *population vector algorithm*. Each cell's preferred direction, baseline rate, and maximum firing rate were obtained, using an adaptive algorithm that randomly initializes these parameters and then iteratively regresses firing rate against target direction (which is assumed to be the intended movement direction) to obtain a closer and closer approximation of their actual values. In subsequent brain-control sessions, these parameters are fixed, and preferred directions are weighted by their respective cells' instantaneous normalized firing rates and summed to obtain a population vector, which is then proportionally converted to instantaneous cursor velocity.

After a period of "fixed" brain control using the preferred directions obtained from the adaptive brain-control session, a subset of the recorded cells (~25%) were given reassigned preferred directions that deviated up to 90 degrees from their original preferred directions. The monkeys were able to perform well on the center-out task despite these changes in the mapping from neural activity to cursor movement. The relative contribution of the cells with the changed mapping was not suppressed; instead, the actual preferred directions of those cells shifted toward their reassigned preferred directions. These shifts were fairly specific to the cells with the new mapping, suggesting that the brain may be able to disentangle and selectively modify each cell's contribution to its global output to accommodate new functions required of the network.

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Mechanisms Underlying Suppression of Axonal Conduction by High Frequency Stimulation

A.L. Jensen and D.M. Durand

Biomedical Engineering Department, Neural Engineering Center, Case Western Reserve University, Cleveland, OH

The effect of deep brain stimulation (DBS), also known as high frequency stimulation (HFS), on neural elements remains an important question. Prior experiments designed to address this question have shown that sinusoidal and square pulse HFS (50-200 Hz) suppresses cellular activity and axonal conduction *in vitro* (Jensen and Durand[1], 2005). HFS of fiber tracts could provide novel, direct control of axonal conduction and seizure propagation within the brain. Yet, the underlying mechanisms of suppression are unknown. In this study, we tested the hypothesis that the mechanisms underlying HFS-mediated suppression of axonal conduction *in vitro* are nonsynaptic.

Compound action potentials (CAP) were recorded extracellularly in the alveus of *in vitro* rat hippocampal slices (N=12). Square pulses (100 _s, 2–4x antidromic threshold, 0.5 Hz) were applied to the alveus to generate the CAP. Field potential amplitude, width, and time to peak were analyzed prior, during, and post HFS (sinusoidal, 50-200 Hz, 20-second duration). HFS experiments were carried out in both normal and synaptic blocker artificial cerebral spinal fluid. Synaptic transmission was blocked using a receptor antagonist cocktail containing 100 _M Picrotoxin (PTX), 50 _M D-(-)-2-amino-5-phosphonopentanoic acid (D-APV), and 40 _M 6,7-dinitroquinoxaline (DNQX).

HFS suppression of axonal conduction (CAP) was dependent on HFS amplitude and frequency, but independent of stimulus duration. In addition, evoked potential (CAP) width and time to peak decreased in response to HFS, indicating an increased synchronization of the underlying units. The frequency dependence map for HFS matches that observed in clinical DBS, with maximal suppression between 50-200 Hz and no suppressive effect below 10 Hz or above 500 Hz. HFS suppression of axonal conduction (CAP amplitude, width, and time to peak) was independent of synaptic transmission. In addition, absence of synaptic transmission produced no significant difference in axonal conduction (CAP) recovery following HFS termination. CAP amplitude returned to pre-HFS amplitudes within 30 seconds of HFS termination. CAP recovery was independent of HFS amplitude and frequency.

These data provide new insights into the effects of DBS on neuronal elements, and show that HFS can block not only cellular neural firing but also activity in the axons of these cells through underlying nonsynaptic mechanisms.

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[1]A.L. Jensen and D.M. Durand, 2005 (in preparation).

Electrodes and Stimulators for Strial Presbycusis

Tim Johnson, Matt Carson, Francis Spelman, Scott Corbett, Ben Clopton, Richard Schmiedt*, Advanced Cochlear Systems, 34935 SE Douglas St., Snoqualmie, WA 98065; *Medical University of South Carolina, 39 Sabin St., Walton Research Building, Room 39, Charleston, SC 29425

Many elderly people experience age-related hearing loss extending from low to high frequencies. The relationship between increased hearing thresholds and the corresponding reduction in the endocochlear potential generated by the stria vascularis in the cochlea is well documented (*strial presbycusis*). Some estimates suggest that between six and seven million elderly suffer from strial presbycusis in the U.S. No treatment, other than hearing aids, is available for them at the present time.

Recent research on animals demonstrates that increasing the endocochlear potential (EP) to its normal value results in bringing hearing thresholds near their normal values. Advanced Cochlear Systems (ACS) is developing a hearing assist device based on this new research. The implanted device will maintain the endocochlear potential at near normal values in the ears of strial presbycusis patients. The device will likely reverse their hearing impairment. This device may also arrest deterioration of the scala media.

ACS is following a phased approach to develop the therapeutic device. We have prototyped a Valve Recitifier System (VRS) to test in animals for durations of a few hours to two weeks. The system is being evaluated at the Medical University of South Caolina, using gerbils as subjects. It can increase EP for more than an hour.

We have tested several surface treatments of electrodes: Pt, Ir and IrO. The prototype uses activated iridium oxide film (AIROF) surface treatments. We are testing sputtered iridium oxide film (SIROF) and electrodeposited iridium oxide film (EIROF) as well (EIC Laboratories, Norwood, MA). The rectifier has been fabricated in a half-wave version; two half-wave rectifiers combine to make a full-wave device.

We continue to study electrode surfaces, test the rectifier system in animals, and plan to produce a miniaturized version of the system. (This work was supported by NIH SBIR Grant R44005531-02).

Hydrogels for Promoting Improved Neuroprosthesis Performance — Protein Delivery and Cell Encapsulation

S. Jhaveri[1], M. Hynd[2], J. Frampton[2], S. Retterer[3], S. Trier[4], J. Williams[4], J.N. Turner[3], W. Shain[3], and C.K. Ober[1]

[1]Department of Materials Science and Engineering, Cornell University, Ithaca, NY
[2]Wadsworth Center, Albany, NY
[3]Department of Chemical and Biomolecular Engineering, Cornell University, Ithaca NY
[4]Department of Biomedical Engineering, University of Wisconsin, Madison, WI

Topic area: Materials and Devices

Micro-machined neural prosthetic devices are being used for recording and stimulating specific targets in the central nervous system. However, the long-term performance of these devices is compromised by cellular encapsulation associated with changes of tissue impedance and recording of neuronal activity. We are developing hydrogels to provide for improved device performance. Hydrogels can be used for controlled release of neurotrophins to protect neurons immediately following device insertion and to promote growth of new processes to electrode sites. Alternatively, they can be used as scaffolds to hold cells that can either release signals to surrounding tissue or to make direct connections to adjacent neurons. For biochemical release, we are investigating different hydrogel formulations. Four different types of 2-hydroxyethyl methacrylate (HEMA) hydrogels have been developed to control the capacity and rates of protein release. Initial tests described the kinetics of 10 K and 70 K fluorescently labeled dextrans. The release profiles of trapped molecules from HEMA differed based on the composition of the hydrogels providing release with half-maximal times of 1-24 hours. To test the biological effectiveness of neurotrophin release, hydrogel-coated devices were loaded with NGF to deliver a range of doses (25-1,800 ng/mL). Loaded devices were placed into individual wells containing PC12 cells, and NGF responses were measured. In order to describe the efficacy of hydrogel-delivered NGF, the ratio of the biological activity recorded and calculated amounts of NGF delivered from the hydrogels was calculated. Biological activity was determined by correlating responses from hydrogel-delivered NGF, with responses measured using increasing concentrations of bath-applied solutions of NGF. These data indicated that a lysine-conjugated form of HEMA provided the greatest biological responses and protein-delivery efficacy. Acrylamide- and alginate-based hydrogels are being tested as scaffolds to make hybrid — biological and micromachined — devices. Tests are being performed to demonstrate long-term cell viability and function.

This work was supported by NIH/NINDS, NS044287.

An Investigation of NADPH Oxidase Activity for Biofuel Cell Power Applications Within the Neurological Environment

Gusphyl Justin[1], Yingze Zhang[3], X. Tracy Cui[1], Mingui Sun[1,2], and Robert Sclabassi[1,2]

[1]Department of Bioengineering, University of Pittsburgh, Pittsburgh, PA
[2]Department of Neurological Surgery, University of Pittsburgh, Pittsburgh, PA
[3]Department of Medicine, University of Pittsburgh, Pittsburgh, PA

Topic area: Neural Prosthesis

Several reports are emerging that provide increased evidence of close links between superoxide generation and a number of neurological pathologies, including stroke, Parkinson's, Alzheimer's, and epilepsy. Oxidative stresses are thought to propagate the debilitating effects of such disorders. A *biofuel cell* based on NADPH oxidase activity was investigated as a potential power source for local electrical stimulation and/or drug delivery in the treatment of the aforementioned medical conditions and their symptoms.

NADPH oxidase has previously been found to mediate electron transfer from intracellular NADPH to extracellular oxygen, resulting in the formation of superoxide, O^{2-}, during respiratory burst in white blood cells (WBCs). This plasma membrane-associated protein complex is notably also expressed in microglia, a major source of superoxide in the neural environment. Our interest lies in determining whether electrons traveling through such a membrane-bound protein complex can be intercepted for subsequent transfer to an interfacing electrode and, ultimately, through an electrical circuit.

Initial studies have been focused on isolated human WBC (neutrophil) activity at a biofuel cell anode. The main objective of these studies is to determine whether electrodes in contact with these biological cells are capable of acquiring electrons derived from the *pentose-phosphate pathway*, the major metabolic pathway involving NADPH. When WBCs were incorporated at the anode of the biofuel cell, current densities between 1.4 and 2.7 _A/cm^2 were achieved in the presence of a 100 _ external load. In the absence of cells, current densities between 0 and 1.1 _A/cm^2 were observed under similar load conditions. Cyclic voltammetry is also used to provide further insight into the electron transfer capacity of the WBCs. Next, a similar study was performed using an *in vitro* glial-cell model, and the results of our investigation are presented here.

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Pulse Mode Optical Sensor for Retinal Stimulation

Gamani Karunasiri

Department of Physics, Naval Postgraduate School, Monterey, CA

Topic area: Visual Prostheses/Materials and Devices

Sight loss can be devastating, yet millions of people with blindness or visual impairment face this challenge every day. Researchers have been trying for more than two decades to produce some form of artificial vision for the blind. Existing artificial vision systems are primarily based on stimulation of either retina or brain with a relatively small array of electrodes utilizing signals from an external camera. As the electrode array size is increased for improving the image quality, feeding of stimulating signals from external electronics becomes relatively complex, in particular for parallel processing of visual information.

One approach to overcome this is to integrate photodetectors and electrodes on a single chip which functions similar to that of a retina. However, a typical photodetector generates only a relatively weak electrical signal and would require additional supporting circuitry for enhancing its strength and pulse coding to stimulate ganglion cell neurons in the retina.

In this abstract, a silicon-based optical sensor is presented that can directly convert incident light into a series of large electrical impulses (> 1V) suitable for directly stimulating retinal ganglion cells. The sensor consists of a silicon-controlled rectifier (SCR) connected in series with a parallel RC circuit. Under an external DC bias, the voltage across the RC circuit showed electrical impulses similar to that of action potentials generated by biological neurons. The generation of pulses is due to a regenerative action within the SCR and the pulse rate (0-1,500 Hz) is found to be strongly dependent on the applied DC bias. The maximum pulse rate is determined by the RC time constant (0.7 ms) of the circuit.

For pulse-mode light sensing, the DC bias across the circuit was adjusted just below the pulsing threshold and the active region of the SCR was exposed to a beam of light. It was found that the pulse rate varied rapidly as the intensity of the light beam was increased. For the SCR used in this experiment, light power of 20 μW on the SCR was sufficient to increase the pulse rate from 0 to 1,500 Hz. Future work involves the design and fabrication of optimized integrated sensor circuits and testing of their ability to stimulate biological neurons.

This work was supported by an NIFR grant from the Naval Postgraduate School.

Speech Prosthesis: Initial Recordings From Broca's Area With the Neurotrophic Electrode in a Locked-In Patient

P.R. Kennedy[1], D. Andreasen[1,2], S. Seibert[1], E.J. Wright[1], H. Mao[3], and P. Ehirim[4]

[1]Neural Signals, Inc., 3688 Clearview Avenue, S110, Atlanta, GA
[2]Georgia Tech, Atlanta, GA
[3]Department of Radiology, Emory University, Atlanta GA
[4]Department of Neurosurgery, Gwinnett Medical Center, Lawrenceville GA

Topic area: Speech Prostheses

We have begun to explore the possibility of restoring direct conversational speech in locked-in subjects. Presently, we are working with a 23-year-old male with a brainstem stroke. MRI shows anatomically intact hemispheres. Functional MRI demonstrates an intact Broca's area during a naming task. We have implanted his Broca's area with a two-channel Neurotrophic Electrode with associated twin amplifiers and FM transmitters powered transcutaneously by an induction coil. Eight single units are now reliably obtained at each recording session.

Phoneme mapping study: We have completed the first attempts to map the recorded neural signals to phonemes. The numbers of neural signals are fixed once the neuropil has grown into the electrode tip in about 4 months. We then began searching for modulations in neural activity as each of the 39 English phonemes were presented to the patient auditorially. He was requested to repeat the phonemes to himself. After the session, he confirmed this repetition by moving his eyes upwards (for 'yes'). Inter-phoneme rest periods acted as controls. Strong modulations of single-unit firings have *not* been seen.

Movement relatedness: We next studied attempted mouth and tongue movements in this severely paralyzed patient. *Weak* modulations in a few units were seen during attempted tongue movements to the right.

Sensory relatedness: Neural activity was not evoked by sensory testing of his face, mouth, or tongue using a light touch via a cotton tip.

Signal conditioning paradigms: Using six of the available eight units, the following paradigms are underway:

[1] **One unit repeat:** Using the phoneme 'da', the subject fires the unit twice in succession to produce 'da da' followed by a 3-second pause. Another unit is used to condition 'ma'. Learning curves illustrate the patient's improving performance.

[2] **Two-unit fixed sequence:** In this paradigm, one unit expresses 'heh' and the other 'lo'. He is learning to fire the units in sequence and then pause, to produce 'hello'.

[3] **Two-unit variable expression:** One unit is designated as 'yes' and the other as 'no'. The patient is asked questions whose known answers can only be either 'yes' or 'no'. He expresses his answer in a variable, but appropriate, form, by increasing the firing rate of one of the units, and decreasing the firing of the other.

Funded by the NIH/NIDCD. Work conforms to IACUC and FDA guidelines. Conflicts of interest for PRK and DA.

Electrical Nerve Conduction Block in Mammalian Nerves

Kevin L. Kilgore[1,2,3] and Niloy Bhadra[3]

[1]Department of Orthopaedics, MetroHealth Medical Center, Cleveland, OH
[2]Louis Stokes VA Medical Center, Cleveland, OH
[3]Department of Biomedical Engineering, Case Western Reserve University, Cleveland, OH

Pathological hyperactivity of neuronal signals, with resulting hyperactivity of muscles or sensory inputs, is the hallmark of numerous disease conditions. In many of these conditions, arresting the conduction of these nerve signals could alleviate the disease effect. One promising method for achieving reversible nerve conduction block is through the application of very high-frequency alternating current near the nerve. This type of nerve block has a rapid onset and is quickly reversible. We have evaluated the effectiveness of this type of block in amphibians and mammals.

Acute *in vivo* experiments were carried out in a rat model to determine the effect of frequency, amplitude, and electrode geometry on the nerve block characteristics. A blocking electrode was placed on the sciatic nerve and motor nerve block was quantified by measuring force output of the gastrocnemius muscle. Continuous sinusoidal waveforms in the range of 10 KHz to 30 KHz were tested.

A complete and reversible conduction block was achieved in all six animals at all six frequencies tested. The voltage range for complete block across all frequencies was 2 to 10 Vpp. The block thresholds are repeatable in each preparation over the time course of the experiment (2 hours). The electrode impedance range was 730 Ohms to 1.8 K Ohms. The corresponding current range was 1 mA to 12 mA (peak to peak). There was a linear relationship between threshold amplitude (in voltage) and frequency (R^2=0.7); higher frequencies required higher amplitudes to achieve complete block. In all cases where a 100% block was achieved, the block was maintained at higher amplitudes, up to the highest amplitude tested (10 Vpp). Depending on the specific parameters for block, there is an onset response when the block is first initiated that produces significant activity in the muscle. The magnitude of the onset response was inversely related to frequency, being least at 30 KHz, and varied inversely with amplitude, being least at 10 Vpp. Therefore, the onset response could be reduced by using a high-frequency, high-amplitude waveform. Further methods for reducing this onset response are currently being examined.

Experiments are ongoing to determine the specific parameters that will be necessary for human use. We have recently initiated a study of the chronic application of the high-frequency waveform in dogs in order to demonstrate the safety of electrical nerve block for long-term use. If successful, this type of nerve block could have multiple applications in the treatment of spasticity and pain.

This work was supported by NIH R01-EB-002091.

Restoration of Hand and Arm Function by Functional Neuromuscular Stimulation

Robert F. Kirsch[1], Dustin Tyler[1], Dawn Taylor[1], Harry Hoyen[2], Patrick E. Crago[1], William D. Memberg[1], P. Hunter Peckham[1], J. Thomas Mortimer[1], Kevin L. Kilgore[2], and Michael W. Keith[2]

[1]Department of Biomedical Engineering, Case Western Reserve University, Cleveland, OH
[2]Department of Orthopaedics, MetroHealth Medical Center, Cleveland, OH

The overall goal of this contract is to provide virtually all individuals with a cervical-level spinal cord injury (SCI), regardless of injury level and extent, with the opportunity to gain additional useful function through the use of functional neuromuscular stimulation (FNS) and complementary surgical techniques.

A major component of this contract is to introduce peripheral nerve cuff electrode technology into upper extremity neuroprostheses. We have set up an in-house nerve cuff electrode manufacturing capability, obtained FDA and IRB approval for chronic human implantation, performed a series of cadaver dissections to determine the needed cuff electrode diameters and optimal location for placing cuffs onto a number of key upper extremity peripheral nerves, developed a surgical tool for safely and quickly placing the cuff electrodes onto the nerves, and completed a series of more than 40 intraoperative tests during which cuffs were placed on nerves to evaluate their viability. We recruited two subjects with cervical SCI who received implants of several cuff electrodes each in July 2005. We will study the performance of these cuff electrodes for several months before integrating them into full upper-extremity neuroprostheses in Fall 2005.

This contract has also extensively used musculoskeletal modeling of the upper extremity and shoulder. Specifically, we have used inverse dynamic simulations to demonstrate that a clinically acceptable neuroprosthesis will be capable of restoring a number of key functional tasks to individuals with high cervical (C1-C4) SCI. We have further used these simulations to choose the optimal muscles to include in this neuroprosthesis, and have determined optimal electrode types (muscle-based or nerve-based) and locations (e.g., distal to certain fascicles whose mechanical effects are to be avoided). We have also used modeling to develop and evaluate an EMG-controlled arm and hand neuroprosthesis for individuals with C5-C6 SCI. Modeling was used both to select optimal paralyzed muscles for stimulation and to select optimal voluntary muscles from which to record EMG control signals.

Other ongoing work includes development of a feedback controller for arm position; an evaluation of potential user command interfaces for individuals with high tetraplegia (via facial EMG, neck EMG, and/or head orientation); evaluation of surgical reinnervation techniques to prevent denervation following SCI; and development of a small telemetry system for interfacing body-mounted or wheelchair-mounted sensors to the neuroprosthesis.

This work was supported by NIH/NINDS N01-NS-1-2333.

Feasibility of Transcutaneous Electrical Stimulation for Controlling Epileptic Seizures

K. Koka[1], A. Nayak[1], W. Besio[1], R. Patwardhan[2], and M. Sahin[1]

[1]Department of Biomedical Engineering, Louisiana Tech University, Ruston, LA
[2]Department of Neurosurgery, Louisiana State University, Shreveport, LA

Topic area: Models and Stimulation Paradigms

Epilepsy is the second most prevalent neurological disorder in the United States, afflicting approximately 15 million Americans of all age groups and approximately 1% of the world's population. Antiepileptic drugs are ineffective up to 30% of the time and up to 50% of those receiving regular medications have major side effects. Surgical resection is an option for some patients, but it is also associated with serious complications.

Electrical stimulation is becoming an accepted alternative treatment, but usually involves implantation of electronics. Here, we report on the use of noninvasive electrical stimulation to control seizures in a rat model. The research focuses on the feasibility of controlling seizures in a rat model with transcutaneous electrical stimulation (TES). TES was first verified with computer models, which simulate the potential induced in the rat brain through inhomogeneous intermediate layers of known thickness and conductivities. The computer models were followed by the development of a four-layered rat 'phantom head' model using agarose.

An intracisternal penicillin model was used to induce seizures in Sprague Dawley rats and TES was applied to test its feasibility in controlling seizures. The onset of tonicclonic seizures usually began within 2 minutes after penicillin injection and if unchecked, lasted up to 90 minutes with convulsions reaching over 50/minute. After TES was applied, there was a significant decrease in convulsion activity (ANOVA, $p<0.006$). On average, the convulsions decreased from 37/minute to less than 17/minute as a result of stimulation.

We also developed computer simulations and phantom head models for humans, which indicated that similar results could be expected in people. Thus, TES for seizure control warrants further investigation.

Motor Control Signal Extraction for Brain-Machine Interfaces in a Rat Model

Lavanya Krishnan, Tim Gilmour, Roger Gaumond, and Ryan Clement

Pennsylvania State University, Philadelphia, PA

Topic area: Brain Computer/Machine Interface

A successful brain-machine interface requires the extraction of robust control signals from the neural activity recorded at electrodes interfacing with the brain. Desirable characteristics of the motor-control signal include reliability, stability, and potential for implementation in an implantable device. To date, several candidate control signals (extracellular recorded action potentials or APs, and local-field potentials or LFPs) have been evaluated with various levels of success. Much of this work has involved monkeys, where it is often difficult to systematically evaluate various extraction algorithms due to the small number of subjects employed in such studies. Our group has been focused on developing an experimental paradigm that employs rats performing a basic motor task to explore the advantages and disadvantages of various control signals (including APs and LFPs) as well as a novel autocorrelation-based method of processing the neural signal to extract information related to the neural energy content. Four Sprague-Dawley rats were trained on a behavioral task that involves a task-related time window corresponding to a decision or intent of movement which is temporally separated from the actual movement. The operant chamber consists of three nose poke holes and a water dispenser above the center hole. Each trial is initiated by turning on the center poke-hole light. The rat is trained to poke and remain in the center hole until the center light goes off. Meanwhile a visual cue is presented, indicating the next target. After the center light is extinguished, the rat must enter the poke-hole corresponding to the visual cue to obtain a water reward. The wait in the center poke (while the left or right lights are turned on) enables the rat to make its decision much before the actual movement and enables us to obtain a control signal which is a clearly premotor 'intent' signal. After the rats were performing the task sufficiently well (~2 weeks), they were implanted with 16-channel tungsten microwire arrays in the motor or premotor cortex using standard surgical techniques. Typical recordings at 2 weeks show multiunit cluster activity as well as individual neural spikes of 200-300 microvolts on many channels. While the rats performed the task, LFPs and APs were recorded simultaneously on all electrodes. Preliminary results from peri-event histograms show a clear modulation of neural firing rates relative to the task. Further offline work is aimed at discerning which signals or combinations of them offer the best predictions of intended movement and provide the best stability over time.

In Vivo *Power Generation for Neural Prosthetics*

David A. LaVan[1], *Narayan Aluru*[2], *Hagan Bayley*[3], *Jeff Brinker*[4], *Scott Feller*[5], *Mark Humayun*[6], *Eric Jakobsson*[2], *Gerhard Klimeck*[7], *Kevin Leung*[4], *Steve Plimpton*[4], *Umberto Ravaioli*[2], *Susan Rempe*[4], *Benoit Roux*[8], *Marco Saraniti*[9], *H. Larry Scott*[9], *and Xinguang Zhu*[2]

[1]*Yale University, New Haven, CT*
[2]*University of Illinois at Urbana-Champaign*
[3]*Oxford University, United Kingdom*
[4]*Sandia National Laboratories*
[5]*Wabash College*
[6]*University of Southern California*
[7]*Purdue University*
[8]*Cornell University*
[9]*Illinois Institute of Technology*

Topic area: Materials and Devices

An *in vivo* power system for neural stimulation is being developed that mimics the power-generating mechanism of *Electrophorous electricus.* Electrocytes from this eel consist of high densities of ion transporters and are efficient at converting chemical energy into electricity—they are often used as a source of ion channels and ion pumps for basic research. We are undertaking a multi-faceted program to simulate the function of these cells and to design and fabricate synthetic, biomimetic, analogs using tools combining nanofabrication, microfabrication, biochemistry, and genetic engineering. Modeling efforts are focused on understanding the behavior of transporters and the behavior of synthetic analogs to transporters, as well as the performance of combinations of transporters at multiple length scales.

The synthetic devices are targeted to meet the energy requirements of a retinal prosthesis that currently uses RF power inductively coupled to an implant—it could power other types of implants with modest energy needs as well. While the power needs of the retinal prosthesis and the power capabilities of the synthetic system remain to be determined, it is possible to estimate the power capability of the synthetic system. Typical ion pump spacing of 40 nm on the membrane of an electrocyte have been reported; a single pump has a current capacity of ~1.6e-17A per pump (the system also uses ion channels, but ions move significantly faster through channels) resulting in ~1 _A of current and ~150 mV with a single layer, 1-cm x 1-cm device. Layers could be stacked in parallel or series (just as in *Electrophorous electricus)* to produce higher current or higher potential as needed for the application.

Membrane technologies that are under development include the use of lipid-free nanoporous membranes, micro- and nano-porous membranes supporting modified lipid membranes, and lipid vesicles inserted into pores within a nanoporous material. Obviously, stabilizing the system is a key component of the development effort.

[This system was conceptualized as part of a discussion at the National Academies/Keck Futures Initiative on "Designing Nanostructures at the Interface Between Biomedical and Physical Systems."]

STN High Frequency Stimulation Results in STN Glutamate Release and Striatal Dopamine Release in the Rat: Potential Mechanism of Action in Parkinson's Disease

Kendall H. Lee, Charles Blaha, Katarina J. Kristic, Frederick L. Hitti, C. Daniel Ansevin, Chris Muly, Brent Harris, J.C. Leiter, and David W. Roberts

Dartmouth-Hitchcock Medical Center, Hanover, NH
University of Memphis, Memphis, TN
Emory University, Atlanta, GA

Introduction: It has been previously shown that subthalamic nucleus (STN) high-frequency stimulation (HFS) results in neurotransmitter release. In the present study, we investigated the hypothesis that the specific neurotransmitters dopamine and glutamate are released in the striatum and the STN, respectively.

Methods: Constant potential dopamine amperometry was performed in the striatum using carbon fiber microelectrodes (o.d. 10 μm, length 500 μm) while direct measurement of glutamate release in the STN was made using a dual enzyme-based electrochemical sensor in the anesthetized rat placed in the Kopf stereotactic head frame. Electrical stimulation (100 μsec pulse width; 1 second to 1 hour pulse duration; 100-2,000 microA or 1-20 volt amplitude; 5-300 Hz frequency) using a bipolar stimulating electrode was delivered to the STN or the area immediately dorsal to STN. In addition, dopaminergic fibers in the region of the STN were labeled using monoclonal antibody to tyrosine hydroxylase (TH) or dopamine transporter (DAT) in rat, ferret, monkey, and human brains to examine the anatomical localization of substantia nigra compacta pathways in relation to the STN.

Results: Stimulation of the STN using either voltage or current isolation resulted in STN glutamate release and striatal dopamine release. Glutamate release reached a plateau after ~5 minutes while dopamine release reached a plateau after ~5 seconds of stimulation. STN glutamate levels remained elevated for the duration of stimulation while the striatal dopamine levels returned to prestimulation levels within 1 second despite the continued application of electrical stimulation. In contrast, similar stimulation of the area just dorsal to the STN resulted in greater striatal dopamine release that was sustained. The monoclonal antibody to TH and DAT stain demonstrated that the dopaminergic fibers were running immediately dorsal to the STN in the rat, monkey, and human brains.

Conclusions: STN HFS increases glutamate release in the STN and dopamine release in the stratum. Stimulation dorsal to the STN caused greater dopamine release than did stimulation within the STN. The presence of dopaminergic fibers immediately dorsal to the STN raises the possibility that these dopaminergic fibers may be stimulated directly to release dopamine. Thus, enhanced neurotransmitter release may be an important mechanism whereby HFS of the STN improves the symptoms of Parkinson's disease.

An Implanted, Stimulated Muscle Powered Piezoelectric Generator

B.E. Lewandowski[1,3], *K.L. Kilgore*[2,3,4], *and K.J. Gustafson*[3,4]

[1]*NASA Glenn Research Center, Cleveland, OH*
[2]*Metro Health Medical Center, Cleveland, OH*
[3]*Department of Biomedical Engineering, Case Western Reserve University, Cleveland, OH*
[4]*Louis Stokes Veterans Association Medical Center, Cleveland, OH*

Implanted electronic devices use batteries that must be replaced or recharged, or transcutaneous power transmission that burdens patients with external equipment. We are developing a piezoelectric generator system to harness power from electrically activated muscle for use as an implantable, replenishable power source. Piezoelectric material is connected between a muscle tendon and bone. Electrically stimulated muscle contractions exert force on the piezoelectric material. The resulting charge is transferred to a storage circuit used to power the stimulator and other devices.

A computational model of the piezoelectric material and storage circuit was built to examine the relationship between input force and output power in terms of system parameters, including material properties and dimensions. Specification of parameters depends on the muscle used to run the system and the available implantation space. The theoretical output power was found for a range of input forces and material dimensions. Results predicted power generation in excess of the input power necessary to electrically activate muscle.

Mechanical forces, corresponding to forces that small human muscles can produce, were applied experimentally to a system containing 0.5 cm^3 of piezoelectric material. The resulting output power increased as the input force increased, ranging two to three orders of magnitude greater than the anticipated input power, even with losses. These results suggest that a piezoelectric generator system could power implanted electronics, and therefore warrants further investigation.

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Location of Stimulation Within the Inferior Colliculus Affects Cortical Responses: Implications for an Auditory Midbrain Implant

Hubert H. Lim and David J. Anderson

Department of Biomedical Engineering and Kresge Hearing Research Institute, University of Michigan, Ann Arbor, MI

Topic area: Auditory Prosthesis

The success and limitations of cochlear implants along with recent advancements in deep brain stimulation and neural engineering have motivated the development of a central auditory prosthesis. Current efforts have focused on the auditory brainstem implant (ABI). However, there is a need for a new implantation site due to the lack of success of the ABI, particularly for neurofibromatosis type II patients. A potential site is the inferior colliculus central nucleus (ICC) (Lim and Anderson, 2003). The ICC is a highly organized tonotopic structure and is more surgically accessible than the cochlear nucleus in humans (Lenarz et al., ARO MWM, 2004).

To assess the potential for an auditory midbrain implant (AMI), we stimulated different regions along the frequency and isofrequency dimensions of the ICC and recorded the corresponding neural activity along the tonotopic gradient and across different layers of the primary auditory cortex (A1) in guinea pigs using multichannel Michigan electrodes. The stimulus consisted of single, monopolar electrical pulses (200 μsec/phase, negative leading phase). Current source density analysis, acoustic-driven response patterns, and histological techniques were used to identify the location of each site.

Overall, ICC stimulation achieved lower thresholds, greater dynamic ranges, and more localized, frequency-specific activation in A1 (layer IV) than cochlear stimulation (cochlear data taken from Bierer and Middlebrooks, 2002). However, we observed that location of stimulation within an isofrequency lamina of the ICC affected these A1 responses. Stimulation of more rostral ICC regions elicited higher driven spike rates, larger evoked potentials, greater spreading (along the tonotopic gradient), and lower thresholds of activation in A1. In fact, stimulation of caudal ICC regions did not elicit any A1 activity (even at our maximum level of 56 μA), which may be indicative of greater inhibitory interactions and/or differences in functional projections compared to more rostral regions.

These results suggest that ICC stimulation may enhance both frequency and level discrimination with reduced energy usage compared to cochlear stimulation. Furthermore, location of stimulation within the ICC may affect performance. Stimulation of more rostral ICC regions may achieve lower perceptual thresholds, but with a cost of greater frequency channel overlap. The lack of activation via caudal ICC stimulation suggests the possible need for more complex stimulation strategies that may require a 3D electrode array.

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Stimulation of the Expiratory Muscles Using Microstimulators

Vernon W.-H. Lin[1,2], Xiaoming Deng[1,2], and Ian Hsiao[1,2]

[1]Spinal Cord Institute, Long Beach VA Healthcare System, Long Beach, CA
[2]Department of Physical Medicine and Rehabilitation, School of Medicine, University of California, Irvine, CA

Respiratory complications constitute a major cause of morbidity and mortality in patients with spinal cord injury (SCI). These complications arise in part due to the loss of supraspinal control over the expiratory muscles and the resultant difficulties in clearing airway secretions effectively. The purpose of the present study is to evaluate the efficacy of lower thoracic spinal nerve stimulation using wireless microstimulators in activating the expiratory muscles.

Studies were performed on nine anesthetized dogs. A thoracic laminectomy was performed on each dog, and was followed by spinal cord transection at T2. A total of 16 microstimulators (supplied by the Alfred Mann Foundation, CA) were inserted percutaneously onto bilateral intercostal nerves about 3 cm distal to the neuroforamen from T7 to L1. The stimulation parameters were a frequency of 20 Hz, pulse width of 200 μs, and stimulation burst of 2 seconds. The stimulation intensities were 3.78, 5.4, 8.1, and 10.8 mA. The pressure-generating capacity of the expiratory muscles was evaluated by the change in airway pressure (Paw), which was produced by the microstimulators during airway occlusion. The expiratory muscles were stimulated supramaximally at functional residual capacity, which was expressed as the corresponding changes in Paw.

As a general trend, the expired pressure generated using the microstimulators increased with increasing intensity and the number of spinal nerves recruited. The maximal expired pressures generated from one, two, three, four, five, six, seven, and eight pairs of spinal nerves were 8.4 ± 0.8, 12.2 ± 1.0, 14.6 ± 1.4, 17.8 ± 1.8, 23.0 ± 1.8, 27.7 ± 2.2, 35.2 ± 2.7, 40.4 ± 2.9 cmH_2O, respectively. Bilateral stimulation of seven (from T8 to L1) and eight spinal levels (from T7 to L1) produced the highest changes in Paw. Stimulation of six or less spinal levels resulted in significantly lower Paw. We conclude: (1) lower thoracic spinal nerve stimulation near the neuroforamen using microstimulators produces significant expired pressure, (2) percutaneous placement of the microstimulators near the neuroforamen is effective in producing expired pressure, and (3) percutaneous placements of the microstimulators for restoring cough may be used as a relatively noninvasive clinical tool for patients with spinal cord injury, and with other neurological or respiratory pathologies.

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Feed-Forward Control of Neuroprosthetic Systems With Multiple Degrees of Freedom

Jose Luis Luján[1] and Patrick E. Crago[1,2,3,4]

[1]Biomedical Engineering Department, Case Western Reserve University, Cleveland, OH
[2]MetroHealth Medical Center, Cleveland, OH
[3]Cleveland Functional Electrical Stimulation Center, Cleveland, OH
[4]Cleveland VA Medical Center, Cleveland, OH

Topic area: Neural Prosthesis

Introduction: We previously developed a method for implementing feed-forward neuroprosthetic controllers for musculoskeletal systems with multiple degrees of freedom[1] through inverse models of the musculoskeletal systems under control. Experimental tests showed poorer performance than expected, which we attribute to redundancy of the data used to develop the inverses. Thus, we automated a method for choosing a single optimal inverse prior to controller training[2]. Our present work involves obtaining this unique inverse solution and training a controller capable of independently controlling coupled degrees of freedom. We evaluate our method by testing the controllers in simulation and experimentally with able-bodied and SCI human subjects.

Methods: For simulation studies, we developed a forward model of static isometric force production at the tip of the thumb, controlled by four muscles. This model, which parallels our experimental model, generates forces in three directions. Muscle activation is modeled as a nonlinear function of the electrical stimulus. Time-varying input-output properties are added by including random noise and a linearly decreasing fatigue factor that scales the maximum muscle force with every muscle contraction[3].

Our general approach is to create an artificial neural network-based time-invariant system model from the time-varying input-output data generated by either simulation or experimentation. This model smoothes the input-output relationships, eliminating their variance. The system model also allows us to generate an arbitrary amount of time-invariant input-output data by means of its interpolation capabilities. We choose unique input-output patterns from these time-invariant data that optimize specific performance criteria, such as minimum co-activation, allowing us to eliminate redundancy and obtain a unique solution. We train an inverse-model, static, feed-forward, artificial neural-network controller with these optimal input-output data.

We first study redundancy by stimulating only a pair of antagonists controlling flexion/extension of the thumb's carpometacarpal joint. We then incorporate coupling by stimulating two additional muscles allowing us to additionally control abduction/adduction.

Results and Discussion: Function restored by neuroprostheses can be improved by allowing independent control of redundant systems with coupled degrees of freedom. We demonstrated the feasibility of our approach with a simplified model of a pair of antagonist muscles controlling one degree of freedom[2]. The system model eliminated redundancy due to noise and the optimization eliminated mechanical redundancy. We expect similar results with the more

realistic simulation model we implemented, which will be followed by experimental tests. The use of neural network controllers allows us to improve generalization of muscle stimulation. Furthermore, this methodology is general enough to be suitable for a wide variety of musculoskeletal systems.

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Magnetic Resonance Imaging and Neural Implants:
Risks, Safety, Compatibility, Tests, and Recommendations

Francisco M. Martinez Santiesteban[1], Douglas C. Nol [1], and David J. Anderson[1, 2]

[1]Department of Biomedical Engineering, University of Michigan, Ann Arbor, MI
[2]Department of Electrical Engineering and Computer Science,
University of Michigan, Ann Arbor, MI

Topic area: Electrodes

Given the powerful diagnostic information provided by magnetic resonance imaging (MRI) and the significant improvements in the quality of life of patients using neural implants, it is important that future neural interfaces do not preclude patients from undergoing this type of imaging study and should not represent any additional risk under MRI environments. Furthermore, the possibility of simultaneous functional MRI (fMRI) and neural recordings or stimulations of neural structures, will certainly open multiple research areas that will help our understanding of the nervous system function.

In this work, we present a 16-channel silicon microelectrode, used for neural recordings and stimulation in animal models, that is MR safe and compatible at 2 Tesla (T) and was successfully tested at 7T and 9.4T. As a passive implant, it complies with the MR compatibility specifications of the American Society of Testing and Materials (ASTM).

Thoroughly tested at 2T, no translational or rotational MR-induced forces, no RF-induced heating, or negligible image artifacts around the connector, the bonding pads, and the electrode itself have been observed. The MR-compatible system has been implanted in the auditory cortex and in the inferior colliculus of Guinea pigs and successfully acquired acoustic-driven neuronal signals. In addition, and despite the size of this type of electrode, we have demonstrated that MRI can be used for the *in vivo* detection of implanted silicon microelectrodes with resolutions of approximately 100x100x400 μm^3 at 2T at reasonable acquisitions times.

Even though this system is intended to be used on short-term experiments in animal models, given a limited life span of the used connector, it represents a solid base for future designs that could be used on humans. In particular, in the process of achieving MR-compatibility, we have compiled a group of tests and recommendations that would be useful for any research group working on the design and development of neural prosthesis and for those responsible for safety considerations of patients undergoing MRI studies. Those tests include translational and rotational forces, MR-induced heating, and image artifacts.

We believe that unfortunate accidents involving MRI and neural interfaces (http://www.fda.gov/cdrh/safety/neurostim.html) should be seriously addressed for the future design and use of neural prostheses that will allow a valuable and safe simultaneous use of these technologies.

This work was supported by NIH/NIBIB Resource Center Grant P41 EB2030 to the Center for Neural Communication Technology at the University of Michigan, and the Center for Wireless Integrated MicroSystems (WIMS), an NSF Engineering Research Center.

Neural Degeneration and Gliosis Due to Electrode Implantation

Jonathan P. Mason[1,2], Ruchi Parekh[3], Nathalia Peixoto[1,2], Nick Chernyy[1,2], Steven L. Weinstein[4], Steven J. Schiff[1,3], and Bruce J. Gluckman[1,2]

[1]Center for Neural Dynamics, Krasnow Institute for Advanced Study, George Mason University, Fairfax, VA
[2]Department of Physics and Astronomy, George Mason University, Fairfax, VA
[3]Department of Psychology, George Mason University, Fairfax, VA
[4]Children's National Medical Center, George Washington University, Washington, DC

Topic: Electrodes

It is becoming increasingly clear from human studies that the implantation of depth electrodes can be associated with functional effects independent of electrical stimulation. Although such findings have been attributed to microlesions associated with electrode implantation, to our knowledge there is no prior work examining the anatomy of such lesions. We present a study of degeneration of neuron cell bodies and processes as well as gliosis associated with depth electrode insertion into the hippocampus of rats.

Two groups of male Sprague-Dawley rats (300 g) were selected. The control group (n=6) was not implanted while the experimental group (n=7) was bilaterally implanted axially within the ventral hippocampus, targeting a point near the tip of the enclosed blade of the dentate gyrus. Electrodes were 0.25 mm in diameter and constructed of stainless steel with or without a thin film of iridium oxide. Implanted animals were allowed free access to food and water for 10 days and then sacrificed and perfused with paraformaldehyde. All brains were sliced and stained with an Amino Cupric Silver stain and Glial Fibrillary Acidic Protein to define neurodegeneration and gliosis, respectively.

We found significant neurodegeneration due solely to electrode implantation, without stimulation, for both electrode materials used (n=7). Electrodes inserted into the white matter of stratum radiatum caused local retrograde Wallerian-like degeneration of CA3 pyramidal neurons associated with transection of their axon collaterals and apical dendritic processes. Considerable degeneration of Schaffer collateral and commissural fibers was also noted in the stratum radiatum and oriens of CA1. Moreover, we found fiber degeneration in the alveus, fimbria, and notably in the distal fornices. In addition to the neurodegeneration, interesting patterns of gliosis were observed in several areas of the hippocampal formation: CA1, CA3, hilus, dentate gyrus, subiculum, and entorhinal cortex. Stereological techniques were used to quantify both the degeneration and astrocyte proliferation.

We present, to our knowledge, the first anatomical description of microlesions associated with the implantation of deep brain electrodes for use in epilepsy control. It is critical to distinguish functional effects of such lesions from the effects (functional or degenerative) from long-term chronic stimulation of deep brain structures.

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A Cochlear Nucleus Auditory Prosthesis Based on Microstimulation

Douglas B. McCreery[1], Robert Shannon[2], Steve Otto[2], Albert Lossinsky[1], Victor Pikov[1], and Leo Bullara[1]

[1]Neural Engineering Program, Huntington Medical Research Institutes, Pasadena, CA
[2]The House Ear Institute, Los Angeles, CA

Topic area: Neural Prostheses

The goal of this project is to develop central auditory prostheses based on arrays of microelectrodes implanted into the ventral cochlear nucleus (VCN) in order to restore hearing to patients in whom the auditory nerve has been bilaterally destroyed. Arrays of eight discrete microelectrodes have been implanted into six patients' arrays after resection of acoustic tumors. In four patients, the penetrating microelectrodes evoked auditory percepts at lower currents than the arrays of macroelectrodes on the surface of the CN.

We are developing an array for implantation into the human cochlear nucleus that has multiple electrode sites distributed along silicon shanks extending from an epoxy superstructure. This design will allow for many more independent microstimulating sites than will be practical with an array of discrete microelectrodes. Six cats have been implanted chronically with arrays with 16 microstimulation sites distributed over 4 silicon shanks. The microstimulating sites are spaced 0.3 to 0.4 mm apart. We have made serial measurements of the neuronal responses (compound action potentials) evoked in the cochlear nucleus, and recorded via an electrode implanted chronically in the contralateral inferior colliculus (IC). In one cat implanted for 330 days, the thresholds of the response from most of the electrode sites in the CN were stable over this interval. Thresholds of the neuronal responses range from less than 5 μA to about 15 μA. Overall, there was a slight tendency towards increasing threshold during the 60 days after implantation, which is consistent with thickening of the gliotic capsule around the silicon shanks We have employed several methods to evaluate the ability of adjacent microstimulating sites to excite separate neuronal populations in the VCN. For serial measurements in the animals with chronic implants, we have used paired-pulse interactions. Over the stimulus current from 0 to 50 μA (0 to 4.5 nanocoulombs/phase), interactions between adjacent stimulating sites ranged from virtually none to very strong, with the least interaction between stimulating sites in the caudal VCN. In acute experiments, multi-unit activity was recorded via a 32-site microprobe inserted along the tonotopic gradient in the IC. Microstimulation from adjacent sites in the VCN at up to 30 μA (4.5 nanocoulombs/phase) induced maximum neurons activity at different depths in the IC, demonstrating that the silicon probes can access the tonotopic organization of the VCN. In patients with cochlear nucleus microstimulation, the thresholds for auditory percepts has ranged from approximately 0.5 to 1 nanocoulomb/phase.

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Functional Microstimulation of the Lumbosacral Spinal Cord

Victor Pikov, Douglas McCreery, Albert Lossinsky, and Leo Bullara

Neural Engineering Program, Huntington Medical Research Institutes, Pasadena, CA

Topic: Neural Prosthesis

The long-term objective of this study is to develop a neuroprosthesis for persons with spinal cord injury who are unable to voluntarily control their bladder function. Our approach is to implant an array of microelectrodes in the S1-S2 spinal cord in order to selectively stimulate the neurons involved in micturition reflexes. These include the sacral parasympathetic nucleus (SPN) containing the cell bodies of the bladder preganglionic parasympathetic neurons, the ventrolateral white matter containing axons of these neurons, and the dorsal gray commissure (DGC) containing the interneurons that inhibit the external urethral sphincter (EUS) motoneurons.

Our results indicate that an array 2.5 mm in length is adequate to span the longitudinal extent of the feline SPN (~2-3 mm) and is of appropriate width (2.4 mm) to target the SPNs on both sides. Each array contains three rows of iridium microelectrodes. Each lateral row of six microelectrodes targets the axons of the SPN motoneurons in the ventrolateral white matter, and the medial row of three microelectrodes targets the interneurons in the DGC. Targeting of the SPN in the dorsoventral dimension remains difficult, due to rapid tapering of the sacral spinal cord, the small size of the SPN, and variability in the size of the sacral cord among animals.

The spinal cord of one cat with an implanted array was transected at low thoracic level in order to evaluate the effectiveness of microstimulation in the absence of supraspinal control of micturition. Stimulation-induced micturition reflexes were tested under light Propofol anesthesia. We found that before and after transection (most recently at 7 months), microstimulation with five individual microelectrodes induced small increases of bladder pressure (6 mmHg) and large decreases of EUS tone (-30 mmHg before and -55 mmHg after transection). Interleaved co-stimulation of these electrodes produced large increases in bladder pressure (-30 to -60 mmHg) and relaxation of the EUS (-60 mmHg) resulting in voiding (drop-by-drop before and short streams after transection). After spinal transection, the stimulation was even more effective without anesthesia and near-complete emptying of the bladder was achieved.

The conclusions from our research are: (1) microstimulation in the sacral spinal cord that produces coincident activation of the bladder motoneurons and inhibitory EUS interneurons can induce micturition in normal cats and in cats with transected spinal cords; and (2) adequate targeting of the DGC can be achieved with the existing arrays, but an array with many more microelectrode sites will be needed for precise targeting of the SPN due to the small size of this nucleus and the variability in the size of the sacral cord segments.

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Intrafascicular Microelectrode Arrays Permit Physiologically Based Activation Paradigms

Daniel McDonnall[1], Gregory A. Clark[1], Brett R. Dowden[1], Andrew M. Wilder[1], Nicholas Brown[2], and Richard A. Normann[1]

[1]Bioengineering Department, University of Utah, Salt Lake City, UT
[2]Orthopaedics Department, University of Utah, Salt Lake City, UT

Poor force gradation and the rapid onset of muscle fatigue are the major obstacles to restoring graceful, enduring movement in paralyzed limbs with a motor neuroprosthesis. Conventional extraneural electrode systems used in functional neuromuscular stimulation applications have relatively non-selective access to the large numbers of individual motor units in paralyzed limbs of spinal cord injury patients, and are thus unable to recruit muscle force in a physiological manner to improve fatigue resistance. Having shown that intraneural microelectrode arrays permit finely graded force recruitment, in this study we investigate the possibility of restoring physiological muscle endurance by interleaving stimulation across multiple electrodes implanted intrafascicularly in the peripheral nerves innervating the muscles in cat hind limb.

We have implanted Utah Slanted Electrode Arrays (USEAs), containing 100 0.5-1.5-mm long penetrating electrodes, into cat sciatic nerve. Contractions evoked by electrical stimulation of the nerve were detected by force transducers and/or intramuscular EMG electrodes.

We performed 12-minute fatigue trials in medial gastrocnemius using single-channel stimulation at 3 Hz and at 24 Hz, as well as with interleaved stimulation across eight electrodes, each stimulated at 3 Hz to produce a composite 24-Hz contraction. Single-channel stimulation at 24 Hz resulted in a 50% reduction from initial starting force in 47 seconds, whereas single-channel stimulation at 3 Hz and interleaved stimulation each resulted in only a 20% reduction from initial starting forces after 720 seconds. In addition to improving fatigue resistance, interleaved stimulation of 8 electrodes at 3 Hz per electrode produced tetanic contractions that were as ripple-free as single-channel 24 Hz.

Having demonstrated the use of physiologically based activation paradigms to achieve finely graded, fatigue-resistant muscle contractions in medial gastrocnemius, we are motivated to explore new array implantation sites to find corresponding numbers of selective and independent stimulation sites for other muscles throughout cat hind limb. Selective activation of hip, knee, and ankle extensors via USEAs implanted in sciatic and femoral nerves may produce joint torques sufficient to evoke functional stance in decerebrated cats. We believe the potentially large number of stimulation sites in these muscles, accessible by intrafascicular microelectrode arrays, will permit the use of stimulation paradigms capable of producing finely graded, long enduring, and high-strength contractions.

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A Flexible Retinal Interface Based on Localized Neurotransmitter Stimulation

Neville Z. Mehenti[1], *Harvey A. Fishman*[2], *and Stacey F. Bent*[1]

[1]*Department of Chemical Engineering, Stanford University, Stanford, CA*
[2]*Department of Ophthalmology, Stanford University, Stanford, CA*

Topic area: Visual Prosthesis

Current retinal prostheses primarily use silicon-based microelectrode arrays to locally depolarize groups of neurons in a field-effect manner. There is great concern, however, over the immune response to chronic electrical stimulation as well as the ability of such a device to maintain intimate contact with excitable cells and harness the biological specificity of retinal circuitry. Since retinal cells communicate primarily through synaptic transmission, we are investigating the feasibility of a flexible retinal interface that mimics this physiological process through localized neurotransmitter delivery.

Soft materials microfabrication methods with poly(dimethylsiloxane) (PDMS) were applied to design retinal interfaces based on chemical stimulation. PDMS membranes with microapertures were fabricated using rapid prototyping methods, and were subsequently aligned and bonded to microfluidic channels. Chemical release through the microapertures, as well as stimulation of retinal ganglion cells (RGCs) cultured on the devices, were monitored using fluorescence techniques. Microfluidic plug injection methods were employed within the channels to minimize neurotransmitter release through the aperture and provide an "on/off" switching mechanism. Microfluidic delivery devices were developed using PDMS microfabrication techniques, and the device properties (membrane thickness, aperture diameter, channel dimensions) could be precisely tailored. Chemical delivery through the microapertures was modulated by the flow characteristics in the underlying microfluidic channel, and the release was monitored in real time using fluorescence microscopy. Primary culture RGCs, which were purified from postnatal rats using immunopanning techniques, were cultured on the microdevices and subsequently stimulated through localized neurotransmitter delivery through the microapertures.

Neurotransmitter-based retinal prosthetic chips are feasible and would not only allow for more physiological stimulation, but may also provide higher resolution stimulation with lower power requirements than current electrically based devices. Our technology could potentially be extended to neural prosthetics in general.

Microsphere Templated PEDOT to Stabilize Electrode-Neural Interfaces

Matt Meier[1], Sarah Richardson-Burns[1], Jeff Hendrix[1], and David Martin[1,2,3]

[1]Department of Biomedical Engineering, the University of Michigan, Ann Arbor, MI
[2]Department of Material Science and Engineering, the University of Michigan, Ann Arbor, MI
[3]Macromolecular Science and Engineering, the University of Michigan, Ann Arbor, MI

Topic area: Electrodes

Microporous films of the conducting polymer poly(3,4-ethylenedioxythiophene) (PEDOT) were polymerized on the surface of gold-coated silicon electrodes using polystyrene latex microspheres as a template. The microspheres were suspended in water and deposited on the surface of the bare gold electrodes before polymerization of the PEDOT. After removing the microspheres, the electrical properties of the PEDOT thin films were investigated using cyclic voltammetry (CV) and electrochemical impedance spectroscopy (EIS). The microporous networks' depths and interconnected channels were confirmed by the use of scanning electron microscopy and a focused ion beam. The effects of the PEDOT networks on neuronal adhesion were tested by plating neurons onto the microporous networks and investigated with fluorescence microscopy.

It was found that deposition of the PEDOT films reduced the electrodes impedance, making it better suited for direct electrical connections with neurons. This drop in impedance can be explained by the much increased surface area of the electrode, due to the templated conductive polymer network. In addition to the improved electrical properties, this network gave a rough porous structure, which increased cell adhesion over the bare gold electrode. It was also found that various sphere sizes and high concentrations of spheres provided a more ordered template network.

Vestibular Prosthetics: Guinea Pigs Show Plasticity Necessary to Acclimate to Baseline Stimulation

Daniel Merfeld[1,2], Wangsong Gong[1], Csilla Haburcakova[1], Richard Lewis[1,2], Jennifer Morrissey[1], and Michael Saginaw[1]

[1]Jenks Vestibular Physiology Laboratory, Massachusetts Eye and Ear Infirmary, Boston, MA
[2]Otology and Laryngology, Harvard Medical School, 243 Charles Street, Boston, MA

Disorders of the peripheral vestibular system are relatively common and often result in severely impaired mobility, blurred vision, and debilitating attacks of vertigo and motion sickness. Presently, little can be done to resolve these symptoms when they are chronically present. While data are limited, prevalence of profound vestibular problems appears about the same as profound hearing loss. Early research in the area of vestibular neuroprosthetics alongside the success of the cochlear implant provides hope that providing motion cues via electrical stimulation may eventually help some patients suffering from severe vestibular impairment. Conceptually, vestibular prostheses are similar to cochlear implants and consist of four principal elements: a power source, motion sensors, a microcontroller, and an electrode. We have developed and tested a vestibular prosthesis that senses yaw angular head velocity and uses this information to modulate the rate of current pulses *chronically* applied to the vestibular nerve via an electrode.

Our goal in this study was to determine if animals could adapt to a unilateral implant that provided constant-rate stimulation to one ear at rest. To investigate this issue, guinea pigs were provided chronic constant-rate stimulation. Reflexive eye responses were recorded to assess the state of disorientation elicited by the prosthetic stimulation. We hypothesized that this chronic constant-rate stimulation would elicit a transient eye movement response (nystagmus) and that mechanisms of neural plasticity would compensate for the presence of this constant-rate stimulation.

Guinea pigs responded with a brisk nystagmus that dissipated in less than 1 day. When the stimulation was removed, a brisk nystagmus in the opposite direction was measured, again lasting about a day. These findings demonstrate neural plasticity elicited by the constant-rate stimulation. When the stimulation was alternately turned on and off weekly, the nystagmus response began to decay more rapidly, eventually decaying just a few seconds after the device was turned on or off. This indicates that with repetitive application of chronic stimulation, the animal learned to adapt rapidly to the stimulation state (on or off). Such "switching" will be important for users of vestibular prosthetics so they do not feel disoriented when they remove the device to sleep, shower, etc.

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Vestibular Prosthetics: Squirrel Monkey Responses Show That Useful Motion Cues Can Be Provided via Modulated Chronic Stimulation

Daniel Merfeld[1,2], Wangsong Gong[1], Csilla Haburcakova[1], and Richard Lewis[1,2]

[1]Jenks Vestibular Physiology Laboratory, Massachusetts Eye and Ear Infirmary, Boston, MA
[2]Otology and Laryngology, Harvard Medical School, 243 Charles Street, Boston, MA

Disorders of the peripheral vestibular system are relatively common and often result in severely impaired mobility, blurred vision, and debilitating attacks of vertigo and motion sickness. Presently, little can be done to resolve these symptoms. While data are limited, prevalence of profound vestibular problems appears about the same as profound hearing loss. Early research in the area of vestibular neuroprosthetics alongside the success of the cochlear implant provides hope that providing motion cues via electrical stimulation may eventually help some patients suffering from severe vestibular impairment. Conceptually, vestibular prostheses are similar to cochlear implants and consist of four principal elements: a power source, motion sensors, a microcontroller, and an electrode. We have developed and tested a vestibular prosthesis that senses yaw angular head velocity and uses this information to modulate the rate of current pulses *chronically* applied to the vestibular nerve via an electrode.

Our goal in this study was to determine if motion information, provided via unilateral stimulation, would yield useful information to squirrel monkeys whose lateral canals had previously been plugged to eliminate normal cues indicating yaw head rotations. A prosthesis circuit was attached to the top of the animal's skull, with a motion sensor aligned with the plane of the disabled lateral canals. The rotation sensor signal was sampled by a microprocesser that used this rotation signal to modulate the rate with which current pulses were applied to the ampullary nerve innervating a horizontal canal. The vestibulo-ocular reflex (VOR) was measured to assess efficacy of the prosthetic information during whole-body rotation in darkness. We hypothesized that the animals would utilize the prosthetic motion cue that we provided and that the brain would adapt to utilize the information when information was provided chronically. We also hypothesized that appropriate responses would not habituate to the chronic presence of prosthetic stimulation such that appropriate responses would no longer be initiated following extended duration chronic stimulation.

We found that a measurable VOR was always present, demonstrating that appropriate responses did not habituate (disappear) even when the stimulation was provided chronically. The VOR changed over time, indicating that the animals adapted to better utilize the prosthetic cues. The VOR responses also varied—in a manner consistent with normal responses—when gravito-inertial cues were provided. This demonstrates that the prosthetic rotational cue was being combined with the signals from the otolith organs in a normal manner.

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Tonotopic Spread of Activation in the Inferior Colliculus Elicited by Intra-Neural Stimulation of the Auditory Nerve

John C. Middlebrooks[1] and Russell L. Snyder[2,3]

[1]Kresge Hearing Research Institute, University of Michigan, Ann Arbor, MI
[2]Department of Psychology, Utah State University, Logan, UT
[3]Epstein Laboratory, University of California, San Francisco, CA

The present state of the art for auditory prosthesis is a cochlear implant consisting of an array of electrodes inserted in the scala tympani. Although demonstrably effective at stimulating the auditory nerve, a scala tympani array lies within a volume of conductive perilymph at a variable distance from the osseous spiral lamina and is separated from excitable neural elements by a bony wall. We are exploring penetrating arrays of intra-neural electrodes inserted directly in the auditory nerve as an alternative means of stimulation.

The experiments were conducted in anesthetized cats. We recorded single- and multi-unit activity from the central nucleus of the inferior colliculus (ICC) using a thin-film, silicon-substrate 'Michigan' recording probe. The probe enabled simultaneous recordings at 32 sites spaced in 100-μm intervals along the tonotopic axis of the ICC. In each animal, we first examined the effects of acoustic stimulation in normal-hearing conditions. Then, we deafened the ear contralateral to the ICC recording sites and tested the effects of electrical stimulation with a conventional scala-tympani implant in monopolar (MP) and bipolar (BP) configurations. Finally, we examined the effects of intra-neural stimulation using a 'Michigan' probe that had 16 sites spaced in 100-μm intervals along a single shank. This stimulating array was inserted into the modiolar portion of the auditory nerve, using a lateral approach through the round window, penetrating the osseous spiral lamina below the spiral ganglion. Stimuli were biphasic electrical pulses, 200 μs per phase.

Initial results show the following characteristics of intra-neural stimulation compared to conventional scala-tympani stimulation: (1) thresholds were substantially lower, ~30 dB lower than MP scala-tympani stimulation and ~40 dB lower than BP; (2) tonotopic spread of activation was substantially more restricted than that for MP scala-tympani stimulation, comparable to the most-restricted BP scala-tympani cases; (3) the dynamic range from threshold to saturation of ICC neuronal firing was wider, roughly 20 dB compared to <10 dB for scala-tympani stimulation; (4) the topographic map of intra-neural stimulation site onto ICC tonotopic site was precise, but was non-monotonic, in keeping with the spiral trajectory of auditory nerve fibers; and (5) intra-neural stimulation provided access to the entire frequency representation, from <1 kHz to 32 kHz.

These early results offer encouragement for the further exploration of intra-neural stimulation as a mode of auditory prosthesis.

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Cicerone: 3D Visualization and Database Software for Stereotactic Neurophysiological Recordings

Svjetlana Miocinovic[1,2], Angela M. Noecker[2], Christopher R. Butson[2], Gary S. Russo[3], Jerrold L. Vitek[3], and Cameron C. McIntyre[1,2,3]

[1]Department of Biomedical Engineering, Case Western Reserve University, Cleveland, OH
[2]Department of Biomedical Engineering, Cleveland Clinic Foundation, Cleveland, OH
[3]Center for Neurological Restoration, Cleveland Clinic Foundation, Cleveland, OH

Topic area: Deep Brain Stimulation

Stereotactic neurosurgery and neurophysiological microelectrode recordings in both humans and monkeys are typically done with conventional 2D atlases and paper records of the stereotactic coordinates for noteworthy recordings. This approach is prone to error because the brain shape, size, and location of subcortical structures can vary between subjects. Furthermore, paper record keeping is inefficient and limits opportunities for data visualization. To address these limitations, we developed a software tool (Cicerone) that enables interactive 3D visualization of coregistered magnetic resonance images (MRI), 3D anatomical nuclei, and the recording microelectrode(s). The software was written using VTK (Visualization Toolkit) and Tcl/Tk, making it portable across platforms, including Windows. Cicerone combines the subject MRI data and either a subject-specific or standardized 3D brain atlas. The more intensive, subject-specific 3D anatomical nuclei are constructed by warping 2D digitized atlas slices to the corresponding MRI slices and reconstructing the 3D anatomical volumes from the warped atlas. Alternatively, a more simplistic standard 3D atlas can be scaled to the subject's MRI. In either case, further refinements to the 3D nuclei geometry and position can be made interactively during the microelectrode mapping. The software can be used in preoperative planning to help select the optimal position on the skull for burr hole (in humans) or recording chamber (in monkeys) placement, to maximize the likelihood of complete microelectrode coverage of the intended anatomical target. Intra-operatively, Cicerone allows entry of the electrode microdrive coordinates enabling real-time interactive visualization of the electrode location in 3D relative to the surrounding anatomy. Recording locations are marked and color-coded according to the nuclei they likely belong to (as determined by the experimenter). Recording locations, along with user comments, are stored into a file customized for upload into a database at the end of the experiment. The purpose of this system is to provide visual feedback during the microelectrode recording process in both clinical and experimental procedures. Cicerone can be linked with our companion software (StimExplorer) to provide guidance in DBS electrode implantation by estimating the volume of tissue activated for a given DBS electrode position, orientation, and stimulation parameter setting. In addition, the database component of the system simplifies the neurophysiological recordkeeping process and allows for advanced data analysis and visualization.

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Deep Brain Stimulation — Theoretical Design of Selective Deep Brain Stimulation Parameters for the Subthalamic Nucleus

Svjetlana Miocinovic[1,2], Martin Parent[3], André Parent[3], Christopher R. Butson[1], Gary S. Russo[4], Jerrold L. Vitek[4], and Cameron C. McIntyre[1,2,4]

[1]Department of Biomedical Engineering, Cleveland Clinic Foundation, Cleveland, OH
[2]Department of Biomedical Engineering, Case Western Reserve University, Cleveland, OH
[3]Centre de Recherche Université Laval Robert-Giffard, Beauport, Québec, Canada
[4]Center for Neurological Restoration, Cleveland Clinic Foundation, Cleveland, OH

Despite the clinical effectiveness of subthalamic nucleus (STN) deep brain stimulation (DBS) in the treatment of Parkinson's disease, the underlying neuronal response linked to therapeutic benefit remains unclear. Therapeutic DBS electrode contacts are typically positioned in the dorsal STN/fields of the Forel (H2)/zona incerta region, making both STN projection neurons and pallidothalamic (GPi) fibers viable candidates as the therapeutic target of the stimulation. We built a comprehensive computational model of DBS to design selective stimulation parameters for activation of either STN projection neurons or GPi fibers of passage. The goal of this model is to provide guidance in experimental studies addressing the therapeutic neural element(s) in STN DBS of parkinsonian macaques.

Our model of STN DBS consists of three fundamental components: (1) a 3D anatomical model of monkey basal ganglia generated by warping a brain atlas to the animal's MRI, (2) a finite-element model of the DBS electrode and resulting electric field, and (3) multicompartment biophysical models of STN projection neurons and GPi fibers of passage. The STN models include a 3D geometry derived from biotin dextran amine-labeled STN neurons of a cynomolgus monkey. The model STN firing during intracellular stimulation matches well with *in vitro* experimental results. The GPi fiber has biophysical mechanisms that accurately represent myelinated axons and its geometry follows the anatomic trajectory of the lenticular fasciculus obtained from axonal tracing experiments. Fifty STN neurons and 30 GPi fibers were positioned within the 3D anatomical model. The DBS voltage field in the tissue medium was calculated for Itrel II stimulus waveforms with the Fourier finite-element method and applied to the neuron models to evaluate their firing response to the stimulation.

Monopolar, cathodic, 1 V, 90 μs, 136 Hz stimulus trains generated varying degrees of selectivity. Electrode contacts deep within the STN activated 70% of STN neurons and only 3% of GPi fibers. Stimulation applied in H2 activated 100% of GPi fibers and only 8% of STN neurons. These results suggest that appropriate selection of the stimulating contact can substantially lead to bias activation of either STN neurons or GPi fibers. Given the common location of therapeutic contacts for clinical STN DBS in H2, our results suggest that GPi fibers may represent an important target of the stimulation.

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15 Channel Wireless Headstage System for Single Unit Rat Recordings

Morizio, J.[1]; Irazoqui, P. [1]; Go, V. [1]; Parmentier, J. [1]; Grlj, S. [1]; Bender, J. [1]; Makgill, S. [1]
Santos, L. [2]; Lehew ,G. [2]; Nicolelis, M. A. L [2]
[1] Triangle BioSystems, Inc., Durham, NC 27703, USA
[2]Duke University Medical Center, Durham, NC 27705, USA

Continuous recording of single-unit neuronal activity is an important tool for studying normal and pathological brain function. Current systems typically tether implanted electronics both to remote data processors and power supplies. The tether constrains the animals' behavior and limits possible experimental designs. Ideally, neural activity could be recorded from behaving animals in a natural and enriched environment. With this poster we present the circuits, layouts and test data for a 15 channel wireless headstage system which includes the headstage transmitter and receiver components. The system was successfully tested in a rat and a macaque monkey implanted with cortical multielectrode arrays. Specifications for the lightweight headstage transmitter and receiver components are also presented.

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Nanostructured Porous Silicon Scaffolds for Enhanced Biocompatibility of Multichannel Microelectrodes

Karen A. Moxon[1] *and Nader M. Kalkhoran*[2]

[1]*Drexel University, School of Biomedical Engineering, Philadelphia, PA*
[2]*Spire Corporation, One Patriots Park, Bedford, MA*

Many different types of microelectrodes have been developed for use as a direct Brain-Machine Interface (BMI) to chronically record single neuron action potentials from ensembles of neurons. Unfortunately, the recordings from these microelectrode devices are not consistent and often last for only a few weeks. For most microelectrode types, the loss of these recordings is not due to failure of the electrodes but most likely due to damage to surrounding tissue that results in the formation of nonconductive glial-scar. Since the extracellular matrix consists of nanostructured microtubules, we have postulated that neurons may prefer a more complex surface structure than the smooth surface typical of thin-film microelectrodes, and have previously shown that a nano-porous silicon surface layer or scaffold (1) can decrease adhesion of astrocytes, (2) can increase extension of neurites from pheochromocytoma cells, (3) does not alter the electrical properties of the recording sites, and (4) does not interfere with proper functioning of the microelectrodes *in vivo*. Since a long-term goal of this project is to use this porous scaffold for drug delivery, we wanted to extend our understanding of this material to determine the effect of increasing porosity on neurite outgrowth.

To further our understanding of the effects of different pore sizes on biocompatibility, we tested the ability of seven different porous silicon surfaces to support the growth of PC12 cells. Our results demonstrated that the increasing porosity increased the neural outgrowth of PC12 cells. These results support our hypothesis that nano-porous silicon may be an ideal material to improve biocompatibility of chronically implanted microelectrodes, and the highly porous nature of the resulting material is well suited for drug delivery of bioactive molecules that can potentially ameliorate the damage from electrode implantation.

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[Index terms – porous silicon, chronic recording, rat, brain, single neuron action potential, multineuron recording, and nanotechnology.]

Design of an Ultra-Low Density Hippocampal Neural Circuit In Vitro *Using Multielectrode Array*

Yoonkey Nam [1] *and Bruce C. Wheeler* [2]

[1]*Department of Electrical and Computer Engineering, University of Illinois at Urbana-Champaign, IL*
[2]*Department of Bioengineering, University of Illinois at Urbana-Champaign, IL*

Topic area: *In Vitro* Study; Dissociated Cell Culture

In vitro ultra-low density neuronal networks with controlled growth can be useful to study neural information processing in small neural populations. The main advantage of this system is that it allows us to design different network structures and test our hypothesis of improved functionality. Here, we present multichannel recording and stimulation studies of hippocampal neurons grown in ultra-low density with defined network structures using a planar-type multielectrode array (MEA).

The desired micropatterned neuronal circuit was created by micro-contact printing cell adhesive proteins. To obtain robust and reliable protein adsorption, the surface of the MEA was chemically modified with epoxy-based organosilane before linking proteins. E18 hippocampal neurons purchased from BrainBits (www.brainbitsllc.com) were plated at the density of 50 ~ 75 cells/mm^2 in serum-free, B27-supplemented Neurobasal medium. Multichannel recording and stimulation were performed after 2 weeks *in vitro*.

Reliable cell-electrode coupling was established and we recorded spontaneous network activity after 17 days *in vitro*. Mean firing rates were ranged between 0.1 Hz to 5 Hz. Most of the electrodes that detected spikes were coupled with cell bodies as opposed to neurites (axons or dendrites). Current pulses of 8 ~ 30 μA (biphasic, pulse width 200 μs, every 2 seconds) stimulated directly coupled neurons (usually somata), and evoked responses were successfully recorded.

We have developed reliable techniques in surface chemistry and cell culture that enabled us to create long-lasting patterned neural circuits on MEAs. Preliminary multichannel recording and stimulation is very promising to study the relation between the form of networks and their related functions. We hope our system can contribute to the ongoing global effort to understand learning and memory in low-level brain structures.

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Automatic Control of Standing Balance Following Spinal Cord Injury (SCI) Through Functional Neuromuscular Stimulation (FNS)

Raviraj Nataraj[1], Ronald J. Triolo[2,3], Robert F. Kirsch[1,2], Musa L. Audu[1,2], and Rudi Kobetic[2]

[1]Department of Biomedical Engineering,Case Western Reserve University, Cleveland, OH
[2]Department of Orthopaedics, Case Western Reserve University, Cleveland, OH
[3]Louis Stokes Cleveland Department of Veteran Affairs Medical Center, Cleveland, OH

Topic area: Neural Prosthesis

This project aims to develop a controller that regulates standing balance following spinal cord injury (SCI) using functional neuromuscular stimulation (FNS). Current standing FNS systems use clinically implement supramaximal, open-loop stimulation schemes that stiffen knee, hip, and trunk extensors to achieve standing. This approach is unresponsive to external perturbations and requires the user to exert significant upper-extremity effort upon an assistive device to make postural corrections. We propose to develop a feedback FNS system using target control variables of center-of-pressure (COP) and trunk acceleration, both of which serve as 3D global indicators of posture under static and dynamic conditions. COP and trunk acceleration can be tracked using force-sensitive and accelerometer-based technologies, respectively. Prior and parallel to experimental implementation, the overall control paradigm will be thoroughly tested in simulation using a comprehensive 3D bipedal computer model.

Currently, we have developed an artificial neural network (ANN) that has been trained in simulation to respond to 3D postural errors by producing changes in muscle activation needed to correct those errors. This ANN serves as the actuator in a controller that acts to maintain center-of-mass (COM) position of the model at its initial set-point. We apply small force perturbations to an initially quiet standing model, whereby an "ankle strategy" to maintain balance would be employed. Results demonstrated the desired controller action following force perturbations to the thorax, with successful return of the COM to its initial position. During subject trials, muscle activations will be translated to muscle stimulation parameters, and COM will be replaced by COP as the target control variable.

To improve dynamic responsiveness, we created another ANN that determines postural errors before they occur, and reconstructed the controller to also minimize these future errors. We have shown the feasibility of creating such a predictor ANN in the laboratory. Trunk acceleration and COP data were collected concurrently during perturbed bipedal standing of able-bodied subjects. Data were then organized for off-line ANN training and testing, such that current and previous trunk acceleration and COP values were used as inputs in order to predict changes in COP at a specified future time instant. ANN output followed actual COP trajectories, with correlation coefficients as high as 0.7 for both anterior-posterior and medial-lateral COP position predicted at 200 msec in the future.

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Initiated Chemical Vapor Deposition of Biopassivation Coatings

W. Shannon O'Shaughnessy, D.J. Edell, and K.K. Gleason

Students, Massachusetts Institute of Technology, Cambridge, MA

Recent advances in the field of neuroprosthetics have brought the possibility of human utilization into the near term. One major barrier to this remains the encapsulation and biopassivation of the implants. Current implant technology still suffers from loss of functionality due to scar tissue buildup at the implant site. In addition, implant coating methodologies currently in use require coating thicknesses of 10-25 μm in order to provide the required electrical insulation. This requirement significantly increases the diameter of the neural probe shanks (often only 50-100 μm when uncoated), and consequently, the amount of neural damage upon implantation.

In this work, a novel biopassivation coating is created using initiated chemical vapor deposition (iCVD). The coating consists of a highly crosslinked organosilicon polymer matrix, which is synthesized directly on the surface of the substrate. This novel material possesses a resistivity on the order of 10^{16} Ohm-cm, allowing for a coating thickness on the order of only 1 μm. In addition, the material is insoluble, flexible, and extremely adherent to silicon substrates. This novel polymer coating has also been demonstrated to retain its electrical properties in a simulated biological environment for 6 months.

Material samples are prepared in a custom-built vacuum reactor. Precursor and initiator species are fed as gases to the reactor, where the initiator is then broken down thermally to create radical species. These species react with the monomer to begin the polymerization process. This approach to thin-film formulation allows greater control of film chemistry than traditional plasma or thermal CVD afford as the reaction pathways available for the monomer are severely limited by the benign reaction conditions. In addition, the substrate temperature is independently controlled, allowing deposition on even the most heat-sensitive substrates.

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Rejuvenation of Chronically Implanted Microelectrodes in the Primary Auditory Cortex of Guinea Pigs

K.J. Otto and J.C. Middlebrooks

University of Michigan, Ann Arbor, MI

Topic area: Electrodes

One goal of utilizing chronically implanted recording probes is to monitor changes in the nervous system over time as a result of some experimental manipulation, such as chronic stimulation with a neural prosthesis. However, the quality of the recordings obtained with the chronically implanted recording probes often degrades over the lifetime of the probe, thereby confounding genuine neural plasticity with changes in recording quality. We have developed a procedure for extending the lifetime of chronically implanted iridium-plated silicon-substrate recording probes. This procedure, hereafter termed 'rejuvenation', involves applying a direct-current bias between an electrode site and a distant ground.

We tested the effects of rejuvenation on recording probes chronically implanted in the primary auditory cortex of guinea pigs. We measured the impedance of the recording probes pre- and postrejuvenation using a 1 kHz sine wave. We also recorded neural responses to acoustic stimuli. Stimuli were pure tones and noise bursts presented at varying intensities. Rejuvenation generally resulted in a > 60% decrease in impedance (typically from ~ 4 MΩ to ~1MΩ). Furthermore, rejuvenation resulted in a ~10% average increase in the signal-to-noise ratio (SNR) of the recorded responses, with the most extreme examples increasing by ~200%.

Microelectrode sites with a larger prerejuvenation SNR tended to exhibit a greater SNR change postrejuvenation. Rejuvenation enabled chronic recordings to be made for more than 70 days. The increase in SNR due to rejuvenation was reflected in the variance of the neural responses to acoustic stimuli. Specifically, the variance across the multisite recoding probe of the threshold for detection of acoustic noise bursts generally decreased with increasing SNR of the recordings, such that recordings with greater SNR produced more consistent physiological measurements.

A Systems Approach for Data Compression and Latency Reduction in Cortically Controlled Brain Machine Interfaces

Kyle E. Thomson, Yasir Suhail, and Karim G. Oweiss

Electrical and Computer Engineering Department, Michigan State University, East Lansing, MI

Augmenting human capabilities with cortically controlled Brain Machine Interfaces (BMI) requires sampling multiple cortical areas with high-density electrode arrays and monitoring the activity of large neuronal aggregates for reliable control. The objective of this research is to reduce delays and bandwidth requirements typically encountered during extracutaneous transmission of recorded neural activity from implantable high-density electronic interfaces.

We propose a systems approach for achieving bit rates within the capability of current biotelemetry technology. First, the redundancy across channels is stripped by spatially decorrelating the "physical" data channels to obtain a relatively smaller number of "principal" channels. Second, compression of the signal energy is achieved by expressing the principal channels using the discrete wavelet transform. This process yields large sparseness on the time base, which enables superior noise suppression, large compactness of the neural signal energy, and reduced overall data throughput.

We illustrate the performance using synthetic data that mimics intracortical recordings of macaque monkey during arm-reach movements. The performance is quantified in terms of the maximum latency observed during real-time transmission (particularly during bursting intervals), the average implant processor 'free' time, and the maximum queue length for fixed data intervals. We compare the performance to two limiting cases: first, when spikes are detected and sorted on chip (transmission of time stamps and class labels), and second, when spikes are detected and the entire spike waveforms are transmitted. Our results demonstrate that the proposed approach yields substantial savings in bandwidth and reduced delays over the 'spike detection' method, and asymptotically approaches the performance of the 'detection and sorting' method. We also illustrate the feasibility of hardware implementation within the chip size and power constraints for implantability requirements.

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Augmenting Information Channels in Cochlear Implants Under Adverse Conditions

April Thompson and Karim G. Oweiss

Electrical and Computer Engineering Department, Michigan State University, East Lansing, MI

Cochlear implant (CI) devices have undergone significant development over the past three decades. Advances in micro- and nano-circuit fabrication, the concomitant development of multi-electrode arrays, and the rapid development of signal-processing technologies and their size and power efficient hardware implementations, have all supported the continuous technical improvement of these devices. Measuring quality gains, however, is a challenging task because of the difficulty in assessing the significance of individual factors, such as neuronal survival rate, electrode insertion depth and alignment, presurgical hearing, and language skills, etc. It is clearly established that performance gains indicated by current CI testing procedures quickly erode in the presence of competing speakers, and of transient and persistent sources of environmental noise, thus persistently mitigated by the poor performance of the current speech-processing technology in adverse conditions.

In this work, we conceptualize and develop a novel signal-processing strategy optimized to evoke appropriate neural activity in CI devices under severe adverse conditions, especially "competing voice" type noises. The proposed approach rests on solid evidence that multiresolution analysis by means of the wavelet transform is extremely efficient in capturing the rapid dynamics of speech signals—an essential constituent for proper speech understanding—while minimizing the masking effects of noise. This is achieved by projecting multiple adjacent speech segments onto a multiresolution space and use classical eigendecomposition analysis to select a set of "best basis" components that contain the information of interest. This allows augmenting the total number of information channels provided to the CI while simultaneously increasing the temporal and spectral specificity of every channel. The advantage of the proposed methodology lies in the inherent adaptation to the nonstationary complex noise to allow scalability to arbitrary number of frequency and space-selective information channels. Moreover, the existence and continuous development of novel design strategies for hardware implementation of the wavelet transform with minimal power and size specifications make it more attractive to inherently fuse the separate hardware and microprocessors constituents in today's CI technology in much fewer units, yet achieving superior performance. We present some preliminary results that illustrate the premise of the new approach.

This work was supported by an intramural grant from Michigan State University.

Bilateral Implanted Upper Extremity Neuroprosthesis With Myoelectric Control

P. Hunter Peckham[3,2,1], Kevin L. Kilgore[1,2,3], Michael W. Keith[1,2,3], Harry Hoyen[1], Ronald L. Hart[2], Anne M. Bryden[3], and Fred W. Montague[3]

[1]Department of Orthopaedics, MetroHealth Medical Center, Cleveland, OH
[2]Louis Stokes VA Medical Center, Cleveland, OH
[3]Department of Biomedical Engineering, Case Western Reserve University, Cleveland, OH

The clinical implementation of a second generation upper extremity implanted neuroprosthesis for individuals with spinal cord injury has been initiated. This second generation neuroprosthesis provides control of grasp, forearm pronation, and elbow extension for individuals who are paralyzed with cervical level spinal cord injury. A key feature of this system is the implantation of both the control and the stimulation source, thus freeing the user of most of the external technology, and adding function while making the system easier to use and more reliable. The implanted stimulator-telemeter (IST-12) consists of 12 stimulation channels and 2 channels of myoelectric signal (MES) acquisition. A single radio-frequency inductive link powers the system, transmits control commands, and receives telemetered data.

To date, four IST-12 devices have been implanted in three spinal-cord injured subjects for hand-arm control, including the first subject to have bilateral IST-12 devices. The bilateral subject has C6 motor function bilaterally. The IST-12 was implanted in the left arm as the first stage of a bilateral implementation. Stimulating electrodes were placed on the muscles of the forearm and hand for grasp, and on the triceps for reach. MES recording electrodes were placed on the extensor carpi radialis longus (ECRL - grade 4 strength voluntarily) and the platysma. The MES signal from the ECRL is used to proportionally control grasp opening and closing. The subject demonstrated use of the neuroprosthesis for a variety of tasks, including eating, drinking, writing, and embroidery. Eleven months after the neuroprosthesis was implemented in the left arm, this subject was implanted with a second IST-12 device in the right arm. Stimulating electrodes were placed on the muscles of the forearm and hand for grasp. In addition, two electrodes were placed on the right rhomboid muscle to provide scapular stabilization for this subject. MES recording electrodes were placed on the ECRL and platysma muscles. This subject has now completed the FES rehabilitation phase and has a functioning bilateral system. She is able to perform multiple bilateral tasks, such as using a fork and knife to cut food and using two hands to screw and unscrew a lid on a jar.

Following these successful results, we are planning to implement additional subjects with bilateral hand systems. The use of myoelectric control in neuroprostheses allows considerable flexibility in the control algorithms that can be utilized. We are continuing to develop new control strategies in which four MES channels can be used for the convenient control of two limbs.

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Electrodeposited Iridium Oxide Electrodes for Low Frequency Non-Pulsatile Stimulation in Chronically Implanted Animals

Nathalia Peixoto[1,2], Nick Chernyy[1,2], Steven L. Weinstein[4], Ruchi S. Parekh[3], Jonathan P. Mason[1,2], Sridhar Sunderam[1,2], Steven J. Schiff[1,3], and Bruce J. Gluckman[1,2]

[1]Krasnow Institute for Advanced Study, , George Mason University, Fairfax, VA
[2]Department of Physics and Astronomy, George Mason University, Fairfax, VA
[3] Department of Psychology, George Mason University, Fairfax, VA
[4]Children's National Medical Center, George Washington University, Washington, DC

Topic area: Electrodes

Low-frequency, non-pulsatile electric fields have been shown to modulate neural activity *in vitro* and *in vivo*. We are currently working to implement neural prosthetics for *in vivo* applications, especially adaptive seizure control, based on this technology. In order to modulate activity in chronically implanted animals with electric fields, stimulation electrodes capable of passing high-charge densities are required, where current is primarily limited by electrochemistry at the electrode surfaces. Here we evaluate performance and safety of electrodeposited iridium oxide electrodes in chronically implanted and stimulated animals.

Procedures were carried out under GMU IACUC approval. Iridium oxide film was electrochemically deposited on stainless steel electrodes. Sprague-Dawley rats (300 g) were bilaterally implanted with hippocampal stimulating (3 mm long x 0.25 mm diameter) and recording (0.125 mm diameter twisted pair) electrodes. Six days after surgery, inter-hemispheric stimulation was applied for 100 hours continuously, using voltage ramps of alternating polarity with maximum ± 0.6 V (voltage controlled) and frequencies from 0.01 to 50 Hz. Control groups were either nonimplanted or implanted, but not stimulated. Rats were then sacrificed, perfused, and histologically evaluated (GFAP and cupric silver) to determine tissue damage in comparison to control groups.

Electrode charge storage capacity (CSC) was measured by cyclic voltammetry. Impedance spectroscopy was also used to characterize EIROF deposition. In order to mimic the *in vivo* situation, electrodes were immersed in 0.9% NaCl and submitted to the stimulation protocol described above. Charge passed per stimulation cycle as a function of frequency was calculated by integrating the electric current through the electrodes over each period of the stimulating waveform. *In vitro* tests showed that bipolar stimulation was capable of passing 400 μC. Immediate postoperative bipolar inter-hemispheric stimulation *in vivo* yielded a CSC of 300 μC. However, after 1 week of stimulation, CSC had decreased to 100 μC.

Electrochemical analysis of charge passed through implanted electrodes with the voltage control stimulation protocol showed that the net impedance through bilateral stimulation found *in vivo* was higher than expected, immediately after implantation, and after the stimulation protocol. We hypothesize that there is significant damage to the electrode surface upon implantation, and that various biofouling processes take place over the course of stimulation.

This limits the amount of current that can be safely passed in deep brain stimulation paradigms. These results are relevant for safety assessment, optimal performance, and design of electrode interfaces for high-charge passing stimulation electrodes.

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Psychophysical Detection Thresholds for Electrical Stimulation of the Inferior Colliculus: Comparison to Cochlear-Implant Thresholds

Bryan E. Pfingst, Jennifer M. Benson, Deborah J. Colesa, Gina L. Su, Sanford C. Bledsoe, Hubert H. Lim, and James A. Wiler

Kresge Hearing Research Institute, Department of Otolaryngology, University of Michigan Health System, Ann Arbor, MI

Topic area: Auditory Prosthesis

Central auditory prostheses are required in cases of deafness where the auditory nerve is absent or inaccessible by cochlear implants (CIs). The inferior colliculus central nucleus (ICC) offers a potentially attractive site for prosthetic stimulation due to its orderly tonotopic organization and relatively good surgical accessibility in humans (Lenarz et al., *ARO MWM*, 2004). Neurophysiological studies (Lim and Anderson, *Proc. IEEE EMBS Conf. Neural. Eng.*, 2003, 193-196; and CIAP, 2005) support the hypothesis that ICC implants should have low current requirements and provide more narrow spatial activation patterns than CIs.

We compared psychophysical detection thresholds obtained with electrical stimulation in the ICC of the guinea pig to thresholds obtained with CI stimulation in the same species and using the same stimulus parameters (200 msec pulse trains, 200 μsec/phase symmetric biphasic pulses, negative leading phase, 250 pps). ICC stimulation was via 16-channel, thin-film penetrating electrode arrays placed along to the tonotopic axis as confirmed by multiunit recordings from each site in the array. CI stimulation was via 6- or 8-channel banded scala-tympani arrays.

In contrast to the case with CI stimulation, electrode configuration (TP, BP, MP) for ICC stimulation had little effect on thresholds, consistent with the hypothesized effect of placing electrodes in close proximity to the target neurons. Contrary to our expectation, psychophysical detection thresholds for monopolar stimulation of the ICC usually fell within the range of thresholds obtained with monopolar CI stimulation. Perhaps this was due to a tradeoff between close proximity to the neurons lowering thresholds and restricted activation patterns raising thresholds. Psychophysical thresholds did not vary systematically across the tonotopic axis of the ICC. They were slightly lower for rostral penetrations than for central or caudal penetrations. Threshold vs. pulse rate functions for ICC stimulation differed from those for CI stimulation at both low (< 200 pps) and high (> 1,000 pps) pulse rates, suggesting distinctly different temporal properties for these two types of implants.

These data, together with results from the neurophysiological studies of Lim and Anderson, support the feasibility of a midbrain auditory prosthesis. Use of multiple sites along the rostral/caudal axis might be advantageous for complex stimulus encoding.

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High Surface Area Carbon Nanotube Felt Electrodes

Thomas S. Phely-Bobin[1], Thomas Tiano[1], Brian Farrell[1], Lois Robblee[2], Dave Edell[3], and Richard Czerw[4]

[1]Materials Technology Group, Foster-Miller, Inc., Waltham, MA
[2]LSR Consulting, Peabody, MA
[3]Innersea Corporation, Bedford, MA
[4]NanoTechLabs, Inc., Winston-Salem, NC

Foster-Miller, Inc., in conjunction with Innersea Technology, NanoTechLabs, and Dr. Lois Robblee, has demonstrated a simple, low-cost process for the fabrication of high-capacitance, low-impedance, and high-surface-area carbon nanotube (CNT) electrodes for use as implantable microelectrodes. Implantable microelectrodes for electrical stimulation of neurons and recording neuronal responses are essential tools for neurophysiologists studying the behavior of neurons in the brain, spinal cord, and peripheral nerve. Critical properties of an electrode interface should include low noise, low impedance, biocompatibility, electrical stability during chronic use, and high-charge capacity. Iridium oxide has all of these properties, and thus has been utilized for significant developments in the neural prostheses area. However, these electrodes have several shortcomings, including high material cost, labor-intensive processing, and deterioration of long-term stability.

The results of electrochemical testing of the CNT electrodes show high capacitance and low impedance. Preliminary testing indicates that the CNT felt electrodes have advantages over state-of-the-art iridium oxide electrodes, in that their highest charge capacity is distributed within the cathodic portion of the water window, exactly where iridium oxide charge capacity is lowest. When the integration of the cathodic part of a CV is done in the potential window from 0.3 V (open circuit) to -0.7 V, at which the electrode will be used, we obtain a value of 38 mC-cm^{-2}. Similar integration for an iridium oxide electrode gives a value of 15 mC cm^{-2}. The high-charge capacity of the CNT felt electrode over the cathodic potential range below 0.0 V is advantageous for electrical stimulation with cathodal current pulses. This is a feature lacking in iridium oxide electrodes, for which most of the charge capacity is accessed over anodic potentials above 0.0 V. In order for iridium oxide electrodes to utilize their charge capacity during cathodal pulses, it is necessary to apply an anodic bias to the stimulation electrode between stimulus pulses. This leads to increased complexity of stimulation circuitry and the possibility of the intermittent occurrence of low DC current, both of which will be avoided with the CNT felt electrodes.

The CNT technology holds great promise for simple low-cost fabrication of high-charge capacity stimulation electrodes and low-impedance recording electrodes.

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Laser Micropatterning of Neurons Into Microenviornments on an Electrode Array

Russell Pirlo

Graduate Student, Department of Bioengineering, Clemson University, Clemson, SC

We have created a system for placing single neurons directly onto the electrodes of a micro-electrode array (MEA) in a 1:1 ratio, and creating a microenvironment for controlled network formation. To deposit the neurons on an electrode, we employ our laser micropatterning system. The automated laser micropatterning system exploits the guidance forces of a weakly focused laser beam. This beam passes vertically through the cell deposition chamber, guiding injected cells toward the substrate. The deposition chamber has been designed to incorporate an MEA as the substrate. The deposition chamber is mounted on a three-axis micromanipulator, which is controlled by a computer running control program. Images of the substrate are captured and processed by the automation software, and image recognition algorithms identify cells and deposition points. Desired cells and their deposition points are manually selected, and the software computes the chamber's movement vectors relative to the stationary laser. An image feedback loop is employed to automatically guide the cell to the selected point (i.e., specific electrodes). Microenvironments are formed by placing PDMS masks over the MEA. These masks contain microholes aligned over the MEA to limit cell migration and create a relatively isolated microenvironment. Microchannels in the mask connect the adjacent microholes to allow for neurite extension, which is necessary for network formation. The geometry and number of microchannels can be varied for selective network configurations. The perimeter of the mask is designed as a barrier, which isolates neurons in the array from a random culture of similar cells, including for conditioning the culture media. Using the laser micropatterning system, we deposit NGF encapsulated biodegradable microspheres into the microenvironment to induce neurite outgrowth. The potential applications of this system include the quick and easy fabrication of hybrid devices, such as biosensors and biocomputers, as well as *in vitro* models for the study of cellular and molecular neurobiology, including neurodegenerative diseases such as Alzheimer's and amyotrophic lateral sclerosis.

Intraoperative Testing of Selective Nerve Cuff Electrodes for Neuroprostheses

Katharine H. Polasek[1], Robert F. Kirsch[1,3], Michael W. Keith[1,2], Harry Hoyen[2], and Dustin J. Tyler[1,3]

[1]Department of Biomedical Engineering, Case Western Reserve University, Cleveland, OH
[2]Department of Orthopedics, MetroHealth Medical Center, Cleveland, OH
[3]Cleveland VA Medical Center, Cleveland, OH

Introduction: The overall objective of this project is to extend the benefits of Functional Electrical Stimulation (FES) and neuroprostheses to higher level tetraplegia (C3/C4). An injury at the C3/C4 level introduces additional technical and medical problems compared to C5/C6 individuals that have been the subjects of past clinical work. The CWRU self-sizing spiral nerve cuff electrode is being used in this project to address the added challenges. This study is the final preparation for the chronic implantation of nerve cuff electrodes in a subject with high tetraplegia. The hypotheses are that human nerves have a higher threshold than seen in the cat, that individual muscles can be selectively activated from the proximal nerve trunk.

Methods: The nerve cuff electrode was tested intraoperatively during upper extremity nerve repair surgeries. The cuff electrode was placed on each nerve using a custom implant tool. The multiple contacts on the electrode allowed the surgeon to stimulate in several places around the nerve to evaluate threshold and selectivity.

Results: The CWRU spiral nerve cuff electrode was tested in 18 subjects. Average thresholds were 110 nC (0.8 mA 140 _s) compared to thresholds in cats reported to be approximately 5 nC (0.5 mA, 10 μs). Preliminary selectivity was demonstrated on six of eight nerves tested.

Discussion: The observed thresholds were an order of magnitude higher than that found in the cat model, but similar to thresholds reported by Veraart et al. (80 nC: 0.8 mA, 100 μs). Some increase in threshold is expected since cat nerve axons have a larger diameter than humans, and thus a lower threshold.

Selective recruitment of a single muscle from a nerve innervating multiple muscles was shown in six subjects. However, the ultimate goal is to selectively activate more than one muscle innervated by one nerve. A more thorough search of the parameter space is required to fully test the selective capabilities of this type of electrode.

Conclusions: This study presents preliminary data supporting the chronic implant of nerve cuff electrodes in a human subject. Based on these trials, it is expected that chronically implanted nerve cuff electrodes may selectively recruit individual muscles in the upper extremity, which can be used for functional restoration of hand and arm function in C3/C4 SCI subjects.

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Extraction and Analysis of the Motor Activity From the Spinal Cord of Behaving Rats

Abhishek Prasad, Mesut Sahin, and Erkan Hamsi

Department of Biomedical Engineering, Center for Biomedical Engineering and Rehabilitation Science, Louisiana Tech University, Ruston, LA

Topic area: Neural Prosthesis/Spinal Cord Computer Interface

Injury at the cervical region of the spinal cord during spinal cord injury (SCI) results in quadriplegia. The brain-computer interface (BCI) is one way of generating a substitute for the lost command signals in quadriplegic individuals. In this project, as an alternative, we are testing the feasibility of recording the voluntary motor signals from the descending tracts of the cervical spinal cord as a means of generating the command signals.

Long Evans male rats (375-400 g) were used. An array electrode consisting of 11 shank electrodes (Cyberkinetics, Inc, UT) and a custom-made, multi-contact, silicone substrate, subdural electrode were implanted chronically at the cervical C5-C6 and C6-C7 levels of the spinal cord. A stretch sensor was implanted in the arm for the measurements of the elbow angle.

Behaviors such as walking, reaching, and cleaning the face with the forelimbs were studied for preliminary analysis as they were easily generated without training. Recordings were made using a Grass amplifier that was interfaced with the computer through a National Instrument's data acquisition card and LabView software. The gain for all channels was 5,000, the sampling rate was 40 kHz, and the filtering range was from 100 Hz to 6 kHz. All the channels were differentially configured with respect to a large reference electrode placed subcutaneously.

Principal component analysis (PCA) was performed on the filtered neural signals. The elbow angle was reconstructed with the rectified-integrated version of the neural signals using linear regression. Multivariate analysis of variance (MANOVA) was performed between the multichannel neural data collected during the extension and flexion of the forelimb during various behaviors. The results indicated that different forelimb functions were discernible from the neural recordings.

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Generation of a Fully Integrated Electrode-Tissue Interface by Polymerization of Conducting Polymer in the Presence of Living Neurons

Sarah Richardson-Burns[1, 2], Jeffrey Hendricks[3], Cynthia Sequera[1], Sarah Spanninga[4], and David C. Martin [1,2,3,4]

[1]Materials Science & Engineering, University of Michigan, Ann Arbor, MI
[2]Regenerative Science Training Program, University of Michigan, Ann Arbor, MI
[3]Biomedical Engineering, University of Michigan, Ann Arbor, MI
[4]Macromolecular Sciences and Engineering Program, University of Michigan, Ann Arbor, MI

Currently, our research is focused on interactions between central nervous system (CNS) cells and conducting polymers towards development of novel biomimetic, bioactive materials and adaptive microelectrodes that facilitate establishment of a fully integrated electrode-tissue interface. Chronic implantation of microelectrodes and neural prosthetic devices in the CNS is associated with tissue injury and inflammation. This results in neuronal loss near electrodes and encapsulation of the device in a high-impedance barrier of glia and immune cells, undermining the goal of maintaining long-term communication with neurons.

Previous studies from our laboratory developed methods for depositing the conducting polymer poly(3,4-ethylene dioxythiophene) (PEDOT) directly onto the electrode sites of MEMS neural probes and for templating micrometer and nanometer scale PEDOT surface features. Recently, we have invented a means of electrochemically depositing PEDOT directly within murine brain tissue and in the presence of cultured neurons with little toxicity to the cells for 120 hours following polymerization. This results in a hybrid live tissue-polymer electrode in which electrically active cells are fully integrated within a conducting polymer network. Cells adhered to or embedded within the PEDOT matrix can be electrically stimulated via the PEDOT as indicated by markers of synaptic activity, including the endocytic vesicle dye FM1-43 and intracellular calcium indicators. We also found that a variety of proteins, including nerve growth factor, collagen, laminin, and poly(lysine) can be incorporated into the PEDOT and detected by FTIR and protein assay. Proteins within the PEDOT can be recognized by neural cells as indicated by increased cell adhesion or neurite extension.

The electrical behavior of novel PEDOT electrodes is characterized by impedance spectroscopy and cyclic voltammetry. The morphology of the hybrid PEDOT-live cell/tissue complexes were visualized by fluorescence, optical, and electron microscopy. Primary cortical cultures and organotypic cortical slice cultures were prepared from E18 and P0 mice, respectively.

It is our hypothesis that both the biocompatibility and electrical signal transduction capacity of neural prosthetic devices and deep brain stimulators can be greatly enhanced by integration with the technology we are developing. Our results, showing that PEDOT can be polymerized around living cells and tissues with little toxicity, suggest that PEDOT networks can be grown within living tissue for the purpose of extending electrodes to contact healthy neurons beyond the halo of dead cells and inflammatory tissue that encapsulates chronically implanted neural prosthetics.

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Optical Stimulation of the Auditory System

Claus-Peter Richter[1], Agnella D. Izzo[2], Joseph T. Walsh, Jr.[2], and Duco E. Jansen [3]

[1]Department of Otolaryngology, Northwestern University Feinberg School of Medicine, Chicago, IL
[2]Department of Biomedical Engineering, Northwestern University, Evanston, IL
[3]Department of Biomedical Engineering, Vanderbilt University, Nashville, TN

In contemporary cochlear implants, the injected electric current is spread widely along the scala tympani and across turns of the cochlea. Consequently, stimulation of spatially discrete spiral ganglion cell populations is difficult. One goal of implant device development is to design cochlear implants that can stimulate smaller populations of spiral ganglion cells. Recently, we introduced **a novel concept, optical stimulation of spiral ganglion cells**, to accomplish extremely discrete stimulation (Richter et al., 2005, *Assoc. Res. Otolaryngol*. 28, 1012; Izzo et al., 2005, *Assoc. Res. Otolaryngol*. 28, 1013). Using an infrared optical source with an *in vivo* animal preparation, compound actions potentials (CAPs) in the auditory nerve were evoked that are qualitatively the same as acoustically evoked CAPs. Control experiments, which were made in long-term deafened animals, showed that auditory responses could only be evoked with light stimuli.

Cochlear implants are intended to be used over many years by the patient and, therefore, the device cannot be harmful to the auditory neurons. However, the use of a laser to stimulate auditory neurons has the potential to damage the cells if laser parameters are not selected properly. To date, only our limited pilot data are available providing safe laser parameters, such as energy, spot size, length of continual stimulation, and placement of the fiber, while stimulating the auditory system.

The present experiments were designed to rigorously establish the parameters that allow the safe use of the optical energy without damaging spiral ganglion cells. It could be shown that (1) laser energy can be increased by at least 30 dB between compound action potential threshold and damage to the nerve, (2) continuous stimulation of time periods up to at least 6 hours do not deteriorate the CAP amplitude significantly, (3) spot sizes of 100 µm provides a sufficiently large stimulation signal to elicit auditory response, and (4) the best results for stimulation is achieved if the fiber is placed directly opposite and in close proximity to the spiral ganglion cells. The experiments did not indicate that the nerve fiber is damaged from long-term stimulation.

A Biocompatible Flip-Chip Bonding Process for Neural Interface System Integration

Loren Rieth[1,2], Siddarth Chakravarty[1], Jui-Mei Hsu[1], Richard A. Normann[3], Reid Harrison[2,3], Florian Solzbacher[1,2,3], Matthias Klein[4], and Hermann Oppermann[4]

[1]Department of Material Science and Engineering, University of Utah, Salt Lake City, UT
[2]Department of Electrical Engineering, University of Utah, Salt Lake City, UT
[3]Department of Bioengineering, University of Utah, Salt Lake City, UT
[4]Fraunhofer Institute for Reliability and Microintegration IZM, Berlin, Germany

Chronically implantable wireless neural interfaces require biocompatible and stable high-density integration of sensing, data processing, communication, and power supply. The objective of this research was to develop a biocompatible wafer-level integration technology for a stacked hybrid assembly of silicon, polyimide, ceramics, and SMD components for the next-generation wireless Utah neural interface. The interface consists of a 100-channel amplifier, data compression, RF communication, power recovery module, 2 60-turn planar coils on a ferrite substrate, SMD components, and a modified Utah Electrode Array (UEA) including a re-routing metallization. The coils can be operated as single coils or switched in parallel or series to modify frequency range and voltage gain.

We have developed a multilevel assembly process using the modified UEA as the base plate. AuSn/Au reflow flip-chip bonding was used to connect the IC to the UEA and Sn soldering for SMD and coil assembly. The biocompatible under-bump metallization (UBM) consists of a sputtered thin-film sequence of Pt/TiW/Pt/Au (TiW) with respective thicknesses of 240/150/250/200/100 nm. The top TiW serves as the wetting stop on leads. Wetting experiments were performed on dummy chips in preparation of the bump deposition. AuSn bumps were deposited on the Al pads of the IC chip. The modules were connected using a reflow process. The Au coils were electroplated on Polyimide foil, assembled on an LTCC ferrite plate, glued to the back of the IC, and connected to the IC using a conductive spacer ceramic and the re-routing on the UEA. Sn(Cu) solder is used to solder the SMDs and the spacer. The Cu appears as Cu6Sn5 phase, which has a highly reduced activity. For protection of the solder connections, a polymer underfiller was used (NAMICS U8433). Stability tests of the underfiller were performed in buffer solution. Alternatively, a 100-μm thick Au/Sn solder ring can be deposited and sealed during the initial flip-chip bond for the mechanical and chemical protection of the interconnects.

The process makes use of the most biocompatible combination of materials; takes into account process compatibility, electrochemical effects, and stability in electrolytic environments; and is a general technology base for high-density interconnects for implantable microdevices.

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Switchable LTCC/Polyimide-Based Thin Film Coils

Loren Rieth[1,2], Siddarth Chakravarty[1], Jui-Mei Hsu[1], Richard A. Normann[3], Florian Solzbacher[1,2,3], Matthias Klein[4], Michael Toepper[4], and Sohee Kim[5]

[1]Department of Material Science and Engineering, University of Utah, Salt Lake City, UT
[2]Department of Electrical Engineering, University of Utah, Salt Lake City, UT
[3]Department of Bioengineering, University of Utah, Salt Lake City, UT
[4]Fraunhofer Institute for Reliability and Microintegration IZM, Berlin, Germany
[5]Fraunhofer Institute for Biomedical Technology IBMT, St. Ingbert, Germany

A high-efficiency integrated power supply is crucial to operating chronically implantable wireless neural interfaces. Inductively coupling electrical power constitutes the most viable power source to date. For operation with low primary coil voltages to improve patient safety, a coil with high-voltage gain and Q-factor has to be accomplished. Prerequisites of these characteristics are high number of coil turns, low resistance, low parasitic capacitance between windings and between coil layers and substrate, and high permeability substrate materials to focus the field lines in the coil. Also, the resonance frequency has to be tuned to the frequency of the transmitting/primary coil.

We have developed the first dual-layer planar coil on a Low-Temperature-Co-fired-Ceramics (LTCC) ferrite substrate. The ferrite material has a permeability of ~200 and roughly doubled the efficiency compared to conventional planar coils. A modular multilayer approach allows stacking of multiple coils for an increased number of turns. Given the lateral dimensions of the new Utah neural interface chip (6.03 x 4.88 mm^2), the coil design was optimized using field simulations. Single- and double-layer coils on various substrates and with varying geometry were simulated and optimized for voltage gain and Q-factor. Furthermore, the affects of misalignment between the primary and secondary coil were simulated. The coil consists of 2 60-turn planar coils on a Polyimide film that are glued to an LTCC platelet using a 20-μm thick epoxy resin layer. The windings are fabricated using Au electroplating and are 15 μm wide, 10 μm high, with spacing of 15 μm. They are connected to the IC-amplifier chip of the neural interface via a re-routing plane on the electrode array and using a conductive spacer ceramic fitting onto an 0402 SMD footprint. To allow tuning of the coil voltage gain and resonance frequency and to compensate for varying parasitic losses, the coil stack can be operated as single coils, or switched in parallel or in series.

We will present the simulation results, optimized design, and fabrication process flow, as well as preliminary coil test data. The modular approach and use of ferrite material may make this a technology base for inductive coupling into implantable devices in general.

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Space- and Power-Efficient Volume-Conduction Communication

Paul A. Roche[1,2], Mingui Sun[1,2,3], and Robert J. Sclabassi[1,2,3]

[1]Department of Neurosurgery, Laboratory for Computational Neuroscience, University of Pittsburgh, Pittsburgh PA
[2]Department of Electrical Engineering, Laboratory for Computational Neuroscience, University of Pittsburgh, Pittsburgh PA
[3]Department of Bioengineering, Laboratory for Computational Neuroscience, University of Pittsburgh, Pittsburgh PA

Topic area: Brain Computer/Machine Interface

Radio frequency (RF) is the most popular method of communicating with implantable devices. However, in a conductive medium, RF cannot be both power- and space-efficient. In order to facilitate implantation, we would like to decrease the dimensions of the antenna. For the antenna to remain efficient, the RF frequency range must be increased. However, transmitting a higher frequency signal in a conductive medium worsens the skin effect, increasing the absorption of the signal in the medium. Volume conduction communication emulates the body's natural means of internal to external communication, and it can be utilized to establish a communication link with implantable devices while realizing power and space efficiency.

By generating a current between two internal electrodes, on opposite sides of the implantable device, we can direct a portion of current to flow across the surface of the body. A voltage difference, proportional to the internal output signal, results between two externally affixed electrodes. The position and shape of the internal electrodes can be chosen to maximize the externally measured signal. The transmitted frequency range must be above that of which the active regions are responsive to, in order to avoid inadvertent stimulation, and low enough to neglect the skin effect.

Wireless multichannel subdural amplifiers have been developed to study the feasibility of volume-conduction communication. The internal antennas consumed minimum space and the medium was found to attenuate the signal less than 20 dB, establishing the feasibility of volume-conduction communication.

This work was supported in part by NIH Grants EB002099 and NS38494, and Computational Diagnostics, Inc.

Appearance and Subsequent Attenuation of Non-Compensatory High-Frequency Eye Movements in Animals Instrumented With a Vestibular Prosthesis

Michael A. Saginaw[1,2] and Daniel M. Merfeld[1,3]

[1]Jenks Vestibular Physiology Laboratory, Massachusetts Eye and Ear Infirmary, Boston, MA
[2]Electrical Engineering and Computer Science, Massachusetts Institute of Technology, Cambridge, MA
[3]Department of Otology and Laryngology, Harvard Medical School, Boston, MA

Topic area: Sensory-Motor and Functional Electrical Stimulation

People who suffer from dizziness might benefit from prosthetic neural electrical vestibular stimulation, but such stimulation might also produce undesired side effects, such as blurred vision caused by inappropriate eye movements due to a vestibulo-ocular reflex (VOR) elicited by the electrical stimulation. The goals of this study were to quantify such non-compensatory eye movements and to determine if they diminish with time.

Four adult male guinea pigs were instrumented with a teflon-coated platinum electrode with the conductive tip placed near the ampullary nerve in the lateral semicircular canal. Other instrumentation included a head cap to hold the electronics that controlled the electrode stimulation current. The head cap was fixed on the subject's head via attachment to a head bolt that was attached to the animal's skull. Finally, an eye was instrumented with a frontal eye coil in order to measure horizontal and vertical eye movements using a search coil system.

In subsequent weeks, the subjects received vestibular electrical stimulation in the form of biphasic charge-balanced current pulses, with a constant interpulse interval of 4 msec (250 Hz). Animal subjects were tested on a regular schedule by placing them in the dark on a device that held the head cap and head stationary; eye position measurements were recorded at 9,000 Hz.

Because pulsatile stimulation of nerves elicits nearly synchronous discharges (as opposed to asynchronous discharges that are normally present), we hypothesized that eye movements would be elicited via the VOR at the pulse frequency of 250 Hz. Indeed, spectral analysis showed such eye movement frequency components with velocity amplitudes as large as 10 deg/sec. These eye movements were not compensatory, since the subject's head was stationary during testing. By monitoring the eye movements over time, we recorded the diminution of the amplitude of these inappropriate eye movements by more than a factor of 10, until the size of eye movement response components at 250 Hz were in the range of normal eye tremor.

To the extent that we can extrapolate the guinea pig animal model to a human patient, we expect vestibular prostheses to first elicit inappropriate eye movements at the biphasic pulse frequency, but we expect that these response components will diminish substantially within hours of initiating the prosthetic stimulation.

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Damage to the Neurovascular Unit During Neuroprosthetic Device Insertion: Vascular Casting and Quantitative Analysis

W. Shain[1], C.S. Bjornsson[1], K.L. Smith[1], G. Lin[2], M.A. Abdul-Karim[2], D. LeBlanc[1], D. Szarowski[1], J.N. Turner[1], and B. Roysam[2]

[1]Wadsworth Center, New York State Department of Health, Albany, NY
[2]Rensselaer Polytechnic Institute, Troy, NY

Sustained reactive responses to neural implants currently stifle the successful long-term use of neuroprosthetic devices in the treatment and study of neurological disease and injury. Formation of a cellular and fibrous sheath impedes communication between neurons and device electrodes and ultimately results in complete isolation of the probe. Although the cross-sectional area of these devices is small, insertion inevitably damages the neurovasculature and disrupts the blood brain barrier, leading to inflammation. These stimuli help trigger the characteristic reactive responses observed after device insertion. Chronically, the formation of a cellular and fibrous sheath surrounding the device is accompanied by neovasculaturization.

In order to study both initial vascular damage caused by device insertion and subsequent repair and angiogenesis, fluorescence-labeled vascular casts were prepared at select times following insertion. Mercox resin laced with rhodamine B was injected at constant pressure following perfusion fixation and allowed to polymerize. Thick tissue slices were stained to label nuclei and Nissl substance to highlight cells associated with the neurovascular unit (NVU), and evaluated using confocal microscopy. The same tissue was then corroded and the resulting vascular casts were imaged using scanning electron microscopy. Confocal images of vascular damage, repair, and proliferation were analyzed using automated segmentation algorithms to quantify differences in vessel diameter and branching patterns, and the relationship of cells, especially neurons, to neighboring blood vessels. These results were compared to the normal interrelationships between each of these elements of the NVU, and were described for each layer of the rat premotor cortex. Immediate damage to the neurovasculature typically resulted in a zone of reduced perfusion, as indicated by incomplete vessel filling up to several hundred micrometers from the insertion site. This zone persisted for at least 24 hours; perfusion was restored by 1 week postinsertion. Not all insertions caused a zone of reduced perfusion, suggesting that other factors, such as damage to pial blood vessels, may play a role in the extent of damage.

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Directed Attachment and Outgrowth of Neurons on Protein-Micropatterned Surfaces

Peng Shi, Keyue Shen, and Lance Kam

Department of Biomedical Engineering, Columbia University, New York, NY

Topic area: Cultured Neural Networks

Capturing *in vitro* the diversity and distribution of biomolecules found in neural tissues will lead to improved multi cell networks for understanding neuron function. This report explores the use of aligned, multicomponent patterns containing neural cell-cell communication proteins in differentially directing the attachment and axon/dendrite outgrowth of cultured neurons.

Glass substrates were micropatterned with 25- to 40-micrometer-wide islands of polylysine using a directed plasma ablation technique. A custom-built aligner was then used to define 5-micrometer-wide lines of Protein A by microcontact printing, connecting the polylysine islands. Chimeric proteins consisting of the extracellular domains of either L1 or N-cadherin fused with a Human IgG Fc domain were then captured from solution onto these lines.

On surfaces containing aligned patterns of polylysine and L1, embryonic rat hippocampal neurons selectively attached to the polylysine features and extended long processes along the interconnecting patterns at 1 day of culture. At 3 days, this selectivity was maintained, the processes were several hundred micrometers in length, and few minor processes were observed. N-cadherin, when co-patterned with polylysine, also promoted outgrowth of processes; at 3 days of culture, processes on the N-cadherin patterns are a mix of axons and dendrites, as probed using a MAP2 antibody. However, neuron bodies were observed along the N-cadherin patterns, suggesting that this protein does not provide a high degree of selectivity between neuron attachment and polarization.

Future studies will canvas other cell-cell communication proteins to identify a repertoire of biomolecules that will allow specification of neuron function. This method for directing neuron function is complementary to the use of pattern geometry, and it is envisioned that the combination of both techniques will lead to the establishment of highly defined neuron networks *in vitro*. Focusing on cell-cell communication protein should lead to new models that capture more complex aspects of neuron function, such as synapse formation and modulation.

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Perceptual Discrimination of Intra-Cortical Micro-Stimulation in Primary Auditory Cortex of Awake Rats

Andrew Sloan[1], Thomas Slavens[2], and Robert Rennaker[1,2]

[1]OU Bioengineering Center, University of Oklahoma, Norman, OK
[2]Aerospace and Mechanical Engineering, University of Oklahoma, Norman, OK

We report the development of a behaving small animal model for studying perception of intra-cortical micro-stimulation (ICMS) in primary auditory cortex (A1). The purpose of these studies is to demonstrate that naïve subjects immediately classify ICMS in A1 as an auditory sensation, and to optimize ICMS stimulation parameters to minimize current density. Subjects are trained on a Yes/No forced-choice paradigm requiring identification of stimuli as either purely auditory or other. Preliminary results from rats trained on auditory vs. visual stimuli and rats trained on auditory vs. auditory/visual compound stimuli show that subjects are capable of performing the task with hit rates well above 90% and have very little bias, c' < 0.2. The paradigm is extremely robust, and subjects will reliably classify novel stimuli correctly, d' > 3.0. Initial results on chronically implanted subjects show that some animals will immediate classify high current ICMS in A1 as an auditory event, but fail to classify, or even detect, lower current levels (<100 _A). However, with training, subjects will reliably detect current pulse trains with amplitudes as low as 10-20 _A. Variations in ICMS pulse train parameters significantly affect detection thresholds, with threshold decreasing with increasing phase duration and increasing train burst width.

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Comparison of Infusion and Diffusion Solute Delivery Using Single-Channel, Single-Port Micromachined Devices

K.L. Smith[1], S. Retterer[2], C.S. Bjornsson[1], J.N. Turner[1], and W. Shain[1]

[1]Wadsworth Center, New York State Department of Health, Albany, NY
[2]Department of Biomedical Engineering, Cornell University, Ithaca, NY

Neural prosthetic device insertion into the brain creates an immediate biological reactive response involving the cellular and vascular components within a 1-mm radius of the device. Chronic use of these devices results in a tightly woven cellular and vascular encapsulation that isolates devices from the brain. Over time, the formation of this dense encapsulation increases the resistance of the stimulating and recording electrodes and they become inoperable. One of our primary aims is to determine events involved in initiating and maintaining these responses with the goal of developing intervention strategies to control such responses. One strategy for controlling tissue responses is through local drug delivery via microfluidic channels. This study compares the efficacy of diffusion and infusion of solute delivery through single-channel, single-port silicon devices. Solute delivery was characterized in both *in vitro* and *in vivo*. *In vitro* delivery tested for both repeatable and sustainable delivery using an aqueous solution of Evans Blue (0.1 M) that was delivered into agarose brain phantoms, then imaged using widefield light microscopy. For *in vivo* experiments, devices were backfilled with a cocktail containing membrane permeable (Hoechst stain) and membrane impermeable (propidium iodide, PI) nucleic acid stains, and then inserted into the neocortex of adult male Sprague-Dawley rats (~1.2 mm below the pial surface). Sustainable infusion rates from microfluidic implants were controlled through a constant backpressure source. For infusion, 1 μl of the cell marker cocktail was delivered using a source pressure of either 5 or 10 psi (infusion rates of approximately 15 and 30 nl/min). For diffusion, devices were inserted and remained in place for a period of time equal to the 5 psi infusion times. Following fixation, 100-μm thick tissue slices were imaged using widefield microscopy. Diffusion and infusion of Hoechst and PI were used to estimate the extent of damage due to insertion and/or pressure from infusion. The addressable tissue volume and the extent of tissue containing apoptotic cells were determined via quantitative fluorescence analysis (Image Pro Plus). After widefield imaging, slices were stained with NeuroTrace and imaged by confocal microscopy. These images were used to determine the cell number and extent of damaged neurons that occurred after insertion and infusion (co-localization of PI and NeuroTrace). Active delivery via low-flow infusion shows a significant improvement in the addressable tissue volume compared to diffusion mediated-delivery methods. Using these delivery methods, we will establish criteria for controlling the reactive responses and improved long-term device performance.

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Localizing the Subthalamic Nucleus During Deep Brain Stimulation Surgery: Comparison of Wavelets Decomposition and Power Spectral Density Techniques

André Snellings[1], Oren Sagher[2], David J. Anderson[3,1], and J. Wayne Aldridge [4]

[1]Department of Biomedical Engineering, University of Michigan, Ann Arbor, MI
[2]Department of Neurosurgery, University of Michigan, Ann Arbor, MI
[3]Department of Electrical Engineering and Computer Science, University of Michigan, Ann Arbor, MI
[4]Department of Neurology, University of Michigan, Ann Arbor, MI

The precise localization of subcortical nuclei is vital to the success of deep brain stimulation (DBS) in treating Parkinson's disease. However, identification of target structures using spike analysis is time-consuming, and the expertise involved in this analysis may limit the widespread availability of these surgical procedures. Monitoring the audio amplified electrode signal is a useful guide to subjective evaluation of electrode location, but the focus of this project is to determine the efficacy of different quantifiable localization parameters for an objective characterization of nuclear boundaries.

Neuronal activity was studied from 15 microelectrode recording tracts taken from 9 patients during DBS implantation at the University of Michigan between 2000 and 2005. The subthalamic nucleus (STN) was localized offline using two techniques. First, the background activity level was calculated using a wavelet decomposition procedure. The background, an integrated representation of electrically active cellular components near the electrode tip, constitutes a potentially useful part of the signal that has traditionally only been assessed subjectively on line, then often discarded. Wavelet analysis is able to isolate the background so that its properties can be objectively measured independent of large amplitude foreground spikes, which can be potentially biased by the proximity of the electrode tip to a particular neuron. For comparison sake, the power spectral density was used to calculate average power over the spectra of interest in each recording (400 Hz to 2 kHz), which yielded a measurable signature of the total power envelope at each recording location.

In all 15 of the tracts examined, the peak values of both the background activity level and the average power were calculated within the clinically identified STN. On a per-tract basis, 94% of the background and power values in the upper quartile of the dataset were found within the clinically identified STN. The background level coefficient identified a more distinct boundary between "STN" and "non-STN" structures than did the power index, though, and also indicated a smaller degree of variance on measurements within a single structure. Thus, though both measures are useful in identifying the clinical target, the evidence suggests that measuring the background level when quantified and separated by this wavelet method is the more accurate indicator.

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Micro-Patterns of Positive Guidance Cues Anchored to Polypyrrole Doped With Polyglutamic Acid: A New Platform for Characterizing Neurite Extension in Complex Environments

Hyun-Kon Song[1], Eileen F. Wang[2], Diane Hoffman-Kim[1,3], and G. Tayhas R. Palmore[1,3]

[1]Division of Engineering, Brown University, Providence, RI
[2]Student, Brown University, Providence, RI
[3]Department of Molecular Pharmacology, Physiology, and Biotechnology, Brown University, Providence, RI

Topic area: Materials and Devices

Nerve growth is modulated *in vivo* by positive (permissive or growth-promoting) and negative (growth-inhibitory) biochemical cues. Also, electric stimulation enhances cell adhesion and controls orientation of neurite extension. To study of the combined effects of those multiple cues on nerve cell growth, we developed a new bioplatform on which the cues were spatially controllable.

The platform consists of three components: a supporting tissue (polypyrrole or pPy); an anchor molecule (poly-L-glutamic acid, pGlu); and biochemical cues (poly-L-lysine, pLys; laminin, Lmn; chondroitin sulfate proteoglycan, CSPG). pGlu was electrostatically incorporated into pPy film during electrodeposition. Biochemical cues were covalently attached to the carboxylic functional groups of pGlu extruding from surface of pPy film by using a two-step conjugation procedure. The pPy platform could be micropatterned into submicron features by taking advantage of a unique property of conductive polymers, namely that they electrodeposit only at surfaces to which a voltage has been applied. Also, the counter gradient of two different biochemical cues could be formed on the pPy platform by using a microfluidic mixer.

The use of pGlu as a site for the covalent attachment of bioactive molecules to a substrate coated with polypyrrole enables several important features. First, the biomolecules of interest are confined to the *surface* of the films of polypyrrole, ensuring that a higher concentration of the bioactive reagent is available to make contact with cells. Second, the surface concentration of the biomolecules of interest will remain constant with time because the biomolecules are attached via covalent bonds instead of physisorption. Third, multilayers of biomolecules can be fabricated by attaching an additional layer to the topmost surface layer via the same conjugation chemistry, which may lead to 3D substrates. Also, the surface concentration of the biomolecules of interest can be specified and controlled accurately.

The micropatterned platforms with a single cue or a gradient of two different cues were used to study the behavior of dorsal root ganglia and cortical or hippocampal neurons. Also, we investigated the effects of applied potential combined with the biochemical cues. The number of cells and the area occupied by neurites were quantified by conventional immunolabeling as well as the enzymatic antibody fragmentation technique that we first introduced.

In-Vivo *Recording of Action Potentials From a Rat With a Brain Implantable Microelectrode/Microelectronic Hybrid Integrated Device*

Yoon-Kyu Song[1], William R. Patterson[1], Christopher W. Bull[1], Arto V. Nurmikko[1], John D. Simeral[2], Matthew R. Fellows[2], Selim Suner[3], John P. Donoghue[2], and Barry W. Connors[2]

[1]Division of Engineering, Brown University, Providence, RI
[2]Department of Neuroscience, Brown University, Providence, RI
[3]Department of Emergency Medicine and Surgery, Brown University, Providence, RI

While passive microelectrode arrays have been successfully used for cortical recording from various mammalian brains, including ongoing trials for humans, it is of practical importance to develop microminiaturized neuroprosthetic devices for interfacing with the brain as monolithic implantable units to eliminate bulky electronics wired to a patient.

In order to accomplish such a neural interface, we have developed a microminiaturized "neuroport" using an analog CMOS IC chip integrated with a silicon-based microelectrode array. A fully scalable, 16-channel, ultra-low power, low-noise CMOS preamplifier array with integral multiplexing was designed and fabricated to accommodate stringent thermal and electrophysiological requirements for implantation in the brain. A hybrid integration technique using high-precision flipchip bonder and a reliable silicone encapsulation method were also developed to fabricate a functional, encapsulated microminiaturized neuroprobe device. The device has been evaluated using various methods, including pseudospike detection and local excitation measurement, and showed suitable characteristics for neural recording.

As a proof-of-concept demonstration, we have acutely implanted our neuroport in the brain of a rat under anesthesia and recorded the neural activity from the somatosensory cortex. Male Sprague-Dawley rats were used, and the anesthesia was induced by Pentobarbitol. During the recording session, anesthetic depth was controlled by monitoring tail-pinch response, corneal reflex, and respiration rate. The monolithic recording device was implanted by a pneumatic impulse inserter, such that the electrode tips reached about 1 mm deep from the surface of brain. Fine adjustment in depth of penetration was made by micromanipulator while audiovisually monitoring neural activities.

Spike-like bipolar action potentials, with characteristic amplitude of 100 μV and duration of 1 ms, were detected and recorded simultaneously from multiple electrodes. The neural activity showed a good correlation to the stimulation on whiskers and posterior skin, and higher rate of busting activity was evoked by such stimuli. The results were verified by a collateral experiment using a passive single-wire electrode. While our current work aims to add further microelectronic processing power as well as novel telemetry schemes to the chipscale integrated unit, including low-power analog-to-digital conversion and fiberoptic-based wide-bandwidth telemetry, this *in vivo* animal experiment clearly suggests the practical prospects of employing chipscale brain implantable components for neural prosthetic applications.

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Continuous 3-D Cortical Control of an Anthropomorphic Robotic Arm Under Direct Visual Feedback

M.C. Spalding[2,3], M. Velliste[1,3], and A.B. Schwartz[1,2,3]

[1]Department of Neurobiology, University of Pittsburgh, Pittsburgh, PA
[2]Department of Bioengineering, University of Pittsburgh, Pittsburgh, PA
[3]Center for the Neural Basis of Cognition, University of Pittsburgh and Carnegie Mellon University, Pittsburgh, PA

There are certain criteria that a cortically controlled prosthetic arm must fulfill before it is of benefit to a paralyzed patient. Some of these criteria are that the patient should be able to calibrate the robot without previous knowledge of natural arm movements, be able to direct the robotic arm to all areas of space, be able to continuously control the location of the robot, be able to do independent motor tasks while controlling the device, and be able to make reaching and retrieval movements that appear natural. To satisfy all of these criteria, we have developed a robot-specific adaptive population vector algorithm (PVA) that has no knowledge of natural arm movements, and whose performance is comparable to the previous virtual reality PVA that was initialized by a regression of normalized firing rates and natural arm movement direction (Taylor et al., 2002). Using the regression coefficients obtained from our adaptive algorithm, a monkey does a 3D bidirectional continuous control feeding task. In this task, food rewards are presented at random positions within the robot workspace. To successfully complete a trial, the monkey must reach for the reward, stabilize the arm for loading, retrieve the reward, and stabilize the arm once again when it reaches the mouth. During this continuous task, the monkey has control of the robotic arm during all phases of movement. The monkey is able to reach to all areas of space from all areas of space, and is able to do this while performing an independent motor task (i.e., chews the previous reward while controlling the robot to reach toward the next reward). The average velocity profile obtained from the magnitude of successive population vectors closely approximates the bell-shaped velocity profile of natural reaches. This robot control system fulfills all the above-mentioned criteria for a functional cortical neural prosthetic. In the future this adaptive robot control system may provide paralyzed patients with a cortical neural prosthetic that is easily controlled and moves naturally.

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Microelectrode Arrays for the Analysis of Conducting Polymer–Neural Network Interactions

William R. Stauffer, Brad A. Randall, and Tracy Xinyan Cui

Department of Bioengineering, University of Pittsburgh, Pittsburgh, PA

Previous research has established conducting polymers as an excellent neural interface material, because their inherent electrical properties provide the necessary low impedance, their customizability through dopant selection allows biomolecule immobilization, and their "switchability" provides a means for chemical release and mechanical actuation. When electrodes coated with CDPGYIGSR-doped PPy are implanted into the brain, significantly more neuron projections are found proximal to the modified electrode sites compared to control. New research shows that a second laminin fragment, the neurite outgrowth promoting domain RNIAEIIKDI, improves the electrical properties of conducting polymers and promotes higher neuron attachment and greater neurite outgrowth than CDPGYIGSR.

The goal of this work is to develop an *in vitro* system for the detailed study of the electronic, morphological, and biological interactions of neural networks with conducting polymers. The first steps are presented here: (1) recording action potentials from neural networks, (2) developing methods for coating the electrodes with low-impedance interfaces that promote intimate neuron-electrode contact by immobilization of neuron-promoting species, and (3) combining neural networks with conducting polymers and attempting to record action potentials.

The MED64 (Panasonic) chip is an array of 64 ITO electrodes. Pt is coated on the ITO to reduce impedance (1 kHz impedance ~ 20 kOhms). Using these arrays, action potentials have been recorded that exceed rms noise by a factor of 10 from a population of primary neurons. Arrays without Pt are used for electrochemical studies with conducting polymers.

A common non-bioactive dopant is poly(styrenesulfonate) (PSS). PPy/PSS coatings were synthesized with varying current densities and charge densities for comparison. The optimal current and charge density was judged by the 1 kHz impedance value of the resulting films. The PPy/PSS film with charge density equaling 400 mC/cm^2 using a current density of 2 mA/cm^2 resulted in 1 kHz impedance values below 20 kOhms. Using the bioactive dopant RNIAEIIKDI, an optimal impedance value below 10 kOhms was achieved using a charge density 4 C/cm^2 and a current density of 40 mA/cm^2. These values are comparable to Pt electrode impedance.

Ongoing research is testing the ability of conducting polymer-modified arrays to detect action potentials with a special emphasis on whether the presence of bioactive molecules located at the electrode site can increase the probability of detecting a signal on the given electrode.

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Volume Conduction for Communication and Power Delivery

Mingui Sun, Daliang Li, Paul A. Roche, Jun Zhao, Brian L. Wessel, and Robert J. Sclabassi

Department of Neurosurgery, University of Pittsburgh, Pittsburgh, PA

Two crucial components are required for almost all implantable neural prosthetic devices, an information link and a power source. The existing approach uses a radio frequency (RF) coupler to meet the requirements. Although successful in several applications, this method suffers from a short operation distance. We investigate a different approach in which the neural implant operates on the volume conduction properties of biological tissue.

For data communication, we have designed a volume conduction antenna which directs electrical current to the location of reception and reduces the undesired current at the site of implant. This design has several desirable features. A working prototype device for animal experiments with a volume conduction communication channel has been constructed in our laboratory. The electronic circuitry, which was encapsulated by epoxy resin, was constructed on a double-sided printed circuit board. The dimensions of the implantable device were approximately 10x12x3 mm. Although this size was relatively large for some neural implants, it can be reduced significantly in the future with large-scale integrated circuits.

We found that volume conduction can also be used to deliver power. Although this represents a new concept for implantable devices, a similar mechanism already exists in nature where electric eel and other aquatic creatures deliver energy by volume conduction. We have conducted a computer simulation study using the finite-element method. Our result shows that the shape of the fish body is important in redistributing and focusing electric power. It is also interesting to observe that the weaponry organs of the strongly electric fish are arranged in a nearly linear form. In order to study the effectiveness of a similar structure in power delivery, we modeled the central slide of a human head as a disk. Two arrangements of power delivery electrodes were compared. In the first case (bipolar case), a pair of electrodes was placed across 1/4 of the disk circumference. In the second case (linear case), we allowed voltage to vary linearly across the same arc length. Under identical current emission in both cases, our simulation indicates that the far-field electric current for the linear case is significantly larger than that for the bipolar case. On the other hand, in the vicinity of the terminal electrodes, the undesirable near-field current is greatly reduced. Our investigation suggests that a biologically inspired volume conduction system could be used to deliver a certain amount of power for implantable devices.

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Sleep-Wake Stage and Behavior Discrimination in Rats Using a Combination of EEG and Head Acceleration Measurements

Sridhar Sunderam[1,2], Nathalia Peixoto[1,2], Nick Chernyy[1,2], Jonathan P. Mason[1,2], Steven L. Weinstein[4], Steven J. Schiff[1,3], and Bruce J. Gluckman[1,2]

[1]Krasnow Institute for Advanced Study, George Mason University, Fairfax, VA
[2]Department of Physics and Astronomy, George Mason University, Fairfax, VA
[3]Department of Psychology, George Mason University, Fairfax, VA
[4]Children's National Medical Center, George Washington University, Washington, DC

Topic area: Brain Computer/Machine Interfaces

Accurate brain state discrimination and the ability to track state transitions are critical for development of continuous feedback algorithms for seizure control. Prior methods for state of vigilance discrimination used EEG spectral measures alone. We show that head acceleration, measured noninvasively, significantly enhances sleep-wake staging and behavior discrimination in rats implanted with bilateral hippocampal depth and cortical EEG electrodes.

Video and EEG were recorded continuously from rats for 7 days using custom-made electronics, which included DC-sensitive, biaxial microelectromechanical system (MEMS) accelerometers in the headstage. An EEG expert inspected video and EEG to classify sequential 15-second epochs from representative 1-hour recordings into different sleep-wake stages: awake, quiet sleep, or REM sleep. Observed behavior in each epoch was also labeled as exploratory, repositioning, eating/drinking/grooming, quiet, or twitching. Spectral power (dB) in select frequency bands (0.5-3.9, 4.0-7.9, 8-12.9, 13.1-50 Hz) was measured in 1-second windows of the EEG (two cortical and two depth) and head acceleration (x and y axes) and averaged over each 15-second epoch. The data were divided into equal training and test segments, and a linear discriminant analysis was performed on the training set using the 24 features.

The leave-one-out classification error for behavioral state was 21.6% ($p<0.01$) using only the 16 EEG features, and improved to 13.6% ($p<0.01$) when acceleration features were included. The error for sleep-wake stage was 9% ($p<0.01$) using only EEG features, but 6.8% ($p<0.01$) when acceleration features were added. Application of the linear classifier to the test data gave significant agreement ($p<0.01$) between predicted and actual states of over 80% for behavior prediction, and over 90% for sleep-wake state prediction.

Including head acceleration measurements significantly improved the ability of EEG to discriminate broad sleep-wake transitions, and could distinguish patterns characteristic of such behavior as grooming, twitching, or feeding. For instance, drinking appeared as a 6-Hz oscillation on the accelerometer, and several drinking episodes were detected (and verified) simply by thresholding the accelerometer signal power in the 5-7 Hz band. This improved behavioral state detection capability will be especially useful in formulating and informing detection and feedback control algorithms for treating seizures.

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Low-Frequency Electrical Stimulation of the Globus Pallidus for Torsion Dystonia

Michele Tagliati[1], Joan Miravite[1], Jay L Shils[2], and Ron L Alterman[1]

[1]Mount Sinai School of Medicine, New York, NY
[2]Lahey Clinic, Burlington, MA

Although low-frequency stimulation (LFS, i.e., <100 Hz) was initially employed to treat dystonia with deep brain stimulation (DBS), most recent results have been obtained using high-frequency stimulation (HFS; i.e., 130 Hz or higher). We report our experience with 12 dystonia patients treated with LFS at the GPi.

Between January and October 2004, we instituted LFS at the GPi in 12 patients with torsion dystonia. Nine patients suffer with primary dystonia, six of which are DYT1+. All patients underwent micro-electrode guided frame-based stereotactic implantation of Model 3387 DBS leads (Medtronic, Inc., Minneapolis, MN). Ten patients were treated bilaterally. Surgical complications included an infection at a PG site in one patient and an extension fracture in another. The Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) was employed to assess the patients' clinical status within 1 week of surgery, at the time of the institution of LFS, and at their last followup visit.

All but two of the patients were initially treated with HFS and subsequently switched to LFS. Seven patients were switched because their response to HFS was inadequate (Group 1). Of these, three suffered with secondary dystonia, two with primary sporadic dystonia, and two with DYT1-associated dystonia who had previously undergone unsuccessful thalamotomy. Within this group of inadequate responders, one patient with primary dystonia experienced a profound and persistent improvement in his motor function soon after the commencement of LFS. None of the patients were significantly worsened by LFS, although one patient's BFMDRS scores slightly deteriorated.

Three patients with primary dystonia (two DYT-1+) who had responded well to HFS were switched to LFS in an attempt to extend battery life (Group 2). Each of these patients has been followed for 12 months with no loss of efficacy.

Finally, two patients with DYT1-associated dystonia were treated with LFS from the outset of therapy (Group 3) and have exhibited improvements in their respective BFMDRS scores that are equivalent to those reported by others for HFS in this subgroup of patients.

These preliminary results, generated from a small, heterogeneous population, suggest that: (1) a trial of LFS should be considered in patients who respond inadequately to HFS; (2) it may be safe to switch HFS responders to LFS in order to extend battery life and reduce stimulation side effects; and (3) LFS may be as effective as HFS in the treatment of DYT-1 associated primary dystonia. LFS should be further evaluated as an alternative to HFS for the treatment of torsion dystonia.

Steerable Trajectory With Optical Guidance: A More Efficient Means for DBS Mapping

Cha-Min Tang and M. Samir Jafri

Department of Neurology, University of Maryland School of Medicine; and Baltimore VA Medical Center, Baltimore, MD

The single most important determinant of success for deep brain stimulation (DBS) is the accuracy of electrode placement. To achieve the necessary positional accuracy, most centers use microelectrodes advanced in parallel tracks to electrophysiologically map the target. An inherent weakness of parallel track strategy is its poor efficiency for detecting the borders that are parallel to the mapping track. It is the position of these most distal side borders that are critical for mapping accuracy. Consequently, multiple tracks are generally required. However, each additional parallel track can displace and injury up to 200 mm^3 of brain tissue by the long, thick guide cannula traversing the frontal lobe. We propose a novel strategy for DBS mapping, whereby the very tip of the probe can be precisely steered to approach the critical lateral borders at a perpendicular orientation with a curved trajectory. The curved trajectory is implemented using shape memory metal (Nitinol) tubing. Computer simulations and *ex vivo* studies suggest that this strategy can provide more accurate target mapping using only a SINGLE track through the frontal lobe. Probe tip steering is well suited for optical guidance using optical coherence tomography in conjunction with software for calculating target position and for displaying the complex 3D structure. The next step is to test this system in primate studies.

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Practical Use of Brain Signals to Control an Upper Limb Neuroprosthesis

Dawn Taylor[12], Thomas Cowan[1], Abirami Muralidharan[1], Stephen Foldes[1], Andy Cornwell[1], Quinn Daniels[1], and Benjamin Rellinger[1]

Department of Biomedical Engineering, Case Western Reserve University, Cleveland, OH
Louis Stokes Cleveland VA Medical Center

We are evaluating the use of both noninvasive and invasively recorded brain activity as a source of command signals for controlling functional electrical stimulation (FES) systems designed to restore arm and hand movements in individuals with spinal cord injury at the C4 level and above. We are also developing strategies to combine brain and EMG-based command signals to optimize control quality and ease of use for all FES users.

Ideally, we would like to be able to accurately extract all aspects of the desired limb movement from the natural brain signals to simultaneously control all degrees of freedom in the paralyzed limb. However, with current technologies, especially noninvasive technologies, it is likely there will be a mismatch in the number of high-resolution command signals a person can generate and those needed to control the reach-to-grasp movements that are essential for activities of daily living. We are working to resolve this mismatch by developing effective strategies to sequentially map the limited command signals to the critical device functions. Our strategy is to: (1) maximize the number and quality of independent proportional commands signals a person can robustly produce by utilizing coadaptive training in a virtual reality environment; (2) develop robust classifier algorithms that can be used to switch control between different movement modes (e.g., move/rest, reach/grasp, hold/release); and (3) develop decoders that rapidly extract movement goal so the limited command signals can be sequentially mapped in an overlapping fashion (e.g., use command signals to define a movement goal position and set the limb in motion; then remap command signals to control hand orientation while the limb is en route to the target).

We have shown that (1) coadaptive decoding rapidly enables subjects to produce proportional command signals with little training, (2) discrete command signals can be reliably extracted for use as mode switches, and (3) reach goal can be decoded early on in an attempted movement. This suggests that effective reach-to-grasp movements can be controlled with current brain recording technologies.

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Sensory and Motor Representation of Triceps Surae Muscles in the Rat Cortex

A.K. Thompson[1], K.L. Smith[1], W. Shain[1,2], L. Chen[1], X.Y. Chen[1,2], J.S. Carp[1,2], and J.R. Wolpaw[1,2]

[1]Wadsworth Center, New York State Department of Health, Albany, NY
[2]Department of Biomedical Science, State University of New York at Albany, Albany, NY

Rats and primates can change the size of triceps surae spinal reflexes in response to an operant conditioning protocol. This change is dependent on the corticospinal tract. As a first step towards studying the supraspinal inputs responsible for this operantly conditioned change, we are mapping the sensory and motor representations of the triceps surae muscles on the cortical surface of the rat to define the inter-animal consistencies and variations of these representations and their relation to each other. More specifically, we are attempting (1) to quantify the strength of representation at different cortical sites in addition to estimating the area of representation, and (2) to obtain maps in relation to bregma. Information on cortical maps will be essential for pursuing our future goal of chronically monitoring cortical neuronal activity, using implanted microelectrode arrays, during spinal reflex conditioning.

After removing a section of skull over the frontoparietal cortex (about 0.5-3.5 mm lateral to midline and from 2.0 anterior to 4.0 mm posterior to bregma), a monopolar microelectrode (impedance 2-5 MΩ) was placed on the dura. Sensory-evoked potentials (SEPs) were elicited by stimulating the posterior tibial nerve via a cuff electrode in the leg contralateral to the cortical recording site. In the same animals, motor-evoked potentials (MEPs) were elicited in the soleus and gastrocnemius muscles in which fine-wire electrodes were implanted for EMG recording. Maps were generated from SEPs and MEPs collected after moving the cortical electrode in 0.5 mm steps.

In all rats studied to date, sensory maps had a peak 2 mm lateral to the midline. The anterior-posterior location of this peak varied across rats. Motor output maps often showed a strong representation 2 mm lateral to the midline at the level of bregma and additional peaks were occasionally observed. Within rats, the sensory and motor maps overlapped to varying degrees; however, areas of peak responsiveness of the two maps frequently differed (5/6 animals). Further mapping study will also include recordings from depth electrodes to clarify the orientation of these maps and aid in targeting the sensory and motor representations of the triceps surae muscles for future electrophysiological study. Histological analyses will monitor tissue damage and aid in correlation of neuron distributions and recorded responses.

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System and Architecture Design for Implantable Neuroprosthetic Devices

K.E. Thomson and K.G. Oweiss

Electrical and Computer Engineering Department, Michigan State University, East Lansing, MI

Topic area: Neural Prosthesis

Advances in microfabrication technology have enabled the integration of high-density microelectrode arrays on a single device for implantable neuroprosthetic applications. Consequently, the need to transmit recorded neural data from an implantable neuroprosthetic device in real-time becomes increasingly demanding. Additionally, wired neuroprosthetic devices are a source of infection and patient discomfort, thus creating the need for wireless communication.

Current signal processing and communication technology is incapable of transmitting raw sampled data within the wireless bandwidth available, due to the limitations of an implantable environment. Because of the sparse nature of neural signals on the time base, an alternative to existing techniques for raw data transmission is to extract the useful information prior to extra-cutaneous transmission. However, this strategy imposes severe limitations on the computational capabilities of the associated signal processing due to chip size, timing, and power constraints.

Certain design criteria allows for low-complexity algorithms to be implemented for implantable neuroprosthetic devices. Neuroprosthesis systems can tolerate delays of several milliseconds, allowing for processing to take place both inside and outside the cortex. Sampling at 20 KHz quantized to 10 bits is adequate to preserve the neural information. Current fabrication processes facilitate the ability to place a package containing several hundred thousand transistors on the head of a high-density recording electrode array.

Recently, new methods for processing neural data have shown that bandwidth restrictions can be overcome by using signal processing algorithms, including spatial filtering and the discrete wavelet transform (DWT). Both algorithms are well suited for implantation due to their low complexity, as well as their ability to reduce the amount of redundant information.

We detail the system and architecture design for a real-time neural signal processor for performing low-complexity, signal-processing algorithms *in vivo*. The architecture is designed for low power and minimal area, while maintaining the streaming flow of neural information.

A Hydraulic Approach to the Development of a Variable Reciprocating Hip Mechanism for the Reciprocating Gait Orthosis

Curtis S. To[1,2], Rudi Kobetic[2], Ronald J. Triolo[2,3], and Robert F. Kirsch[1,2]

[1]Department of Biomedical Engineering, Case Western Reserve University, Cleveland, OH
[2]Louis Stokes Cleveland Department of Veterans Affairs Medical Center, Cleveland, OH
[3]Department of Orthopaedics, Case Western Reserve University, Cleveland, OH

Topic area: Neural Prosthesis

The hybrid-orthosis system (HOS) is an assistive gait device for individuals with paraplegia that combines the stability of an exoskeleton, with limb mobility controlled via functional neuromuscular stimulation. The HOS incorporates the reciprocating-gait orthosis (RGO), which facilitates reciprocal gait by coupling hip extension with contralateral hip flexion. Hip reciprocation is, however, fixed at a 1:1 flexion/extension coupling ratio (FECR), limiting hip flexion to the extent of contralateral hip extension. This study focuses on examining the feasibility of utilizing a hydraulic system that can couple the hips at variable FECRs.

The proposed design of the hydraulic system uses hydraulic cylinders to transfer moment between the hips and solenoid valves to control the variable FECRs. A prototype was developed using off-the-shelf components to test the efficacy of this design. Optimal cylinder and valve specifications were determined by calculating the cylinder pressures, flow rates, and C_v factors during gait for a series of stock cylinder bore sizes using dynamic data from a 3D computer model of the HOS that incorporated an RGO with 1:1 hip FECR. Optimal mounting configurations of the cylinders relative to the hip joint were determined to minimize pressure and C_v factor. The effect of pulsing a solenoid valve on the cylinder piston velocity at varied frequencies and pulse widths was examined as a technique for achieving variable hip coupling.

The prototype demonstrated the soundness of the proposed hydraulic design by verifying that hip coupling could be readily engaged and disengaged, and each hip could be locked and unlocked independently. Maximum pressures and C_v factors during gait indicate that cylinders with bore diameters between _ and 1 inch and pressure ratings of at least 500 psi at specific mounting configurations could be used for the variable reciprocating hip mechanism. Also, the solenoid valves must have a C_v of at least 0.12. The valve-pulsing test indicates that the piston velocity is indirectly proportional to pulse width. Current work centers on the bench testing of the hydraulic hip mechanism with the optimal mounting and components, and able-body testing of the new orthosis.

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Psychophysical Testing of Non-Spatial Percepts in Macaque V1

P.R. Troyk[1], D. Bradley[2], M. Bak[3], S. Cogan[4], R. Erickson[2], Z. Hu[1], C. Kufta[5], D. McCreery[6], E. Schmidt[7], S. Sung[2], and V. Towle[2]

[1]Pritzker Inst. Biomed. Sci. & Eng., Illinois Institute of Technology, Chicago, IL
[2]University of Chicago, Chicago, IL
[3]Microprobe, Inc., Potomac, MD
[4]EIC Laboratories, Norwood, MA
[5]Frederick, MD
[6]Huntington Medical Research Institutes, Pasedena, CA
[7]Easton, MD

In the field of cortical visual prosthesis research, the historical approach for system design has been to assume a collection of phosphenes, possibly in a grid pattern, from which the artificial perception of an image is to be induced. One problem with this approach stems from the present limitation in electrode technology, which restricts the number of electrodes that might be safely implanted. We estimate that it would be feasible to implant 300–1,000 microelectrodes on the occipital pole and along the medial face. It has not been previously demonstrated that a relatively small number (<1,000) of phosphenes could actually be integrated to form the perception of an image. Owing to the fact that the primate visual system naturally uses many more features, other than spatial ones, for the construction of the perception, it has been previously suggested that using the implanted electrodes to induce features other than spatial ones might, in principle, allow for more sophisticated communication of the artificial visual information to the cortex. We have recently begun tests on a nonhuman primate model to test this hypothesis.

The receptive field (RF) locations were mapped and the orientation tuning was measured for each of 96 activated iridium-oxide intracortical electrodes chronically implanted into the caudal portion of the right operculum of a rhesus monkey. Owing to the natural cortical summation of many orientation cues to form an overall perception, an orientation task, rather than a phosphene task, was devised for testing the theory that stimulation over multiple electrodes can summate. We have designed a two-alternative forced choice task based upon orientation. The animal will carry out the task using inter-stimulus angles of various sizes. From this, we will be able to calculate d', our basic estimate of sensitivity (performance).

Visual response data (firing rates) for the 96 channels were fit with a sliding 2D Gaussian to estimate the midpoint and the tuning width of the receptive field, and fits converged for 89 of the 96 electrodes. RFs were well defined on 89 channels, with centers ranging from -9° to -2° horizontally and 1° to 5° vertically. Sixty-eight channels showed significant orientation tuning ($p<.05$, anova) under the assumption that both unidirectional and axial direction tuning both constitute an orientation preference.

Presently, the animal has been trained in a visual version of the electrical stimulation task through display on a computer monitor. Testing of the animal's response to the multi-percept orientation-based electrical stimulation is in progress.

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Optimizing Incorporation of Hydrogels Into Neuroprostheses — Surface Coating and Selected-Site Deposition

S. Trier[1], S. Jhaveri[2], S. Retterer[3], C. Bjornsson[4], D.R. Kipke[5], C.K. Ober[2], J. Williams[1], J.N. Turner[4], and W. Shain[4]

[1]Department of Biomedical Engineering, University of Wisconsin, Madison, WI
[2]Department of Materials Science and Engineering, Cornell University, Ithaca, NY
[3]Department of Biomedical Engineering, Cornell University, Ithaca, NY
[4]Wadsworth Center, Albany, NY
[5]Department of Biomedical Engineering, University of Michigan, Ann Arbor, MI

We have developed a family of hydrogels for incorporation into micro-machined neural prosthetic devices. These hydrogels can be used for delivery of drugs, neurotrophins, or other proteins, or as cages for cells. Such cells can function as production sites for necessary protein products, e.g., neurotrophins, or as biological components for making improved device/brain connections. We are investigating several different strategies for incorporation of hydrogels onto micromachined devices using uniform surface coatings or site-directed deposition. Surface coatings are subject to shear during insertion, and possible continued stress due to micromotion generated between inserted devices and brain tissue. Alternatively, hydrogels can be deposited in wells or holes micromachined into or through devices, thus protecting hydrogel deposits from shear and deformation. Uniform hydrogel coatings can be achieved by dipping and painting. Site-directed deposition can be achieved using conventional photolithography, two-photon lithography, or printing. Two-photon lithography has great potential since hydrogel structures can be controlled in three dimensions with great precision. Two-photon lithography will also permit layer-by-layer formation, making it possible to control the cross-linking density in each layer. Using this method, we have produced solid objects as well as objects with internal reservoirs. Printing involves the use of piezo-driven micro-nozzles to deliver small amounts of hydrogel to specific locations on the probe. This technique has several advantages, most notably in the speed of hydrogel printing and the flexibility of delivering multiple hydrogel types during the same process through the use of multiple print heads.

Initial testing of hydrogel-containing devices will be made using *ex vivo* device insertion into rat brain slices. Fluorescently labeled hydrogels will be used and real-time images collected during insertions to describe the integrity of the hydrogels. The best device designs will then be used for insertions into intact rat brains, with evaluations of device integrity at different times after insertion. Results from these experiments will provide essential information for determining the most favorable methods for incorporating hydrogels and micromachined devices. Together with new results concerning protein delivery, we will be prepared to design a new generation of devices that should ensure prolonged, consistent high performance of inserted neural prosthetic devices.

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Design, Experimental Testing, and Simulation of In Vivo *Photostimulation/RecordingProbe*

Ubong Ime Udoekwere, Yu-li Liang, Graham Ellis-Davies, Frank Ko, and Simon Giszter

School of Biomedical Engineering, Drexel University, Philadelphia, PA

Topic area: Deep Brain Stimulation/Neural Prosthesis

We have developed a photolysis system for fast *in vivo* uncaging of caged neurotransmitters in the CNS that we are testing in the rat cortex. The system currently consists of a dual-delivery probe that provides controlled microscale injection of caged compounds, as well as regulated delivery of laser light pulses into target cortical tissues. Alongside the delivery features, the probe also integrates a neural recording capability. We aim to accomplish this with a form factor feasible for acute cortical placement and the possibility of chronic placement in the future.

The light/drug delivery portion of the probe consists of a 100-um optical fiber quartz core pulled to a 20-30-um point and inserted into an O-ringed sealed micropipette holder lumen with a finely tapered micropipette in place. Caged material is introduced into the lumen and coupled to a Picospritzer, which regulates microinjection of caged material in the vicinity of the fiber tip and recording site. A DPSS UV laser light source is coupled into the fiber optic probe and regulated using a gating pulse system to deliver approximately 0.1 microJoule per laser pulse at the fiber tip. This arrangement provides a robust device for acute experiments and avoids problems of trace hydrolysis effects we encountered in bath application of caged transmitter during early development.

In parallel with this development, colleagues at Drexel-Materials Engineering Lab (Ko) have developed a braiding and weaving system suited for braiding six fine tetrode wires onto the probe for recording extracellular activity at or near the delivery site in the cortex. The functionality of this recording setup has already been tested separately.

We originally tested the response recruitment of the photolysis uncaging system used directly and alone in rat motor cortex. We found the results to be variable, but statistically significant. This suggested cortical state variations strongly influenced the uncaging effects. Accordingly, we have focused on threshold and response modulation effects of the uncaging. We tested these effects with electrical stimulation in conjunction with uncaging. Subsequent preliminary data using MNI-Glu and GABA with this joint electrical/photostimulation setup have clearly shown that we can bias cortically the circuits significantly: we alter the chronaxie-rheobase curves obtained by electrical stimulation alone. To understand the impact of fiber design, light train delivery, and threshold modulation in the pyramidal circuitry, we have simulated our experimental design. We developed a model that simulates the effect of joint electrical/photolytic stimulation on a single cortical pyramidal cell using NEURON and Matlab. The modulation/bias seen in the simulated responses of the cell model are similar in order to what we have obtained experimentally.

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Ethical Issues in Deep Brain Stimulation Research: Perspectives of Surgical Researchers Studying Parkinson's Disease

Dorothy E. Vawter[1], Karen G. Gervais[1], Angela W. Prehn[1], Thomas B. Freeman[2], Raymond G. De Vries[3], J. Eline Garrett[1], and Timothy Q. McIndoo[1]

[1]Minnesota Center for Health Care Ethics, Minneapolis, MN
[2]University of South Florida, Tampa, FL
[3]St. Olaf College, Northfield, MN

Surgical interventions for Parkinson's disease (PD) and other movement disorders provoke questions of surgical research ethics. We conducted focus groups or individual interviews with 48 North American surgical researchers studying PD to gain insight into their perspectives on surgical research ethics, including placebo-surgery controls, the capacity of subjects to consent to participate, and provisions necessary to respect and protect subjects.

Researchers participating in our study protested that it is unethical that surgeons and patients routinely are forced to make surgical decisions with insufficient information. They attributed this ethical lapse to the culture of surgical research that has traditionally driven studies to resemble therapy as much as possible. Traditional disincentives to conduct rigorously controlled surgical trials include ethical discomfort with high-risk research, the inclination to benefit ill subjects, and the unavailability of research funds except via third party payer claims.

Participants identified uncertainty and disputes about surgical research ethics as a major barrier to the design and conduct of high-quality trials of surgical interventions. They reported frustration with IRBs, study sections, and funding agencies that lack expertise in surgery and surgical research ethics. These review bodies are often reluctant to approve rigorously controlled surgical trials on account of their uncertainty, or disagreement with surgical researchers, about the ethical appropriateness of randomization, blinding, placebo controls, and the like.

The participants asserted that greater scientific precision in surgical trials is ethically required and that rigorously controlled surgical trials are appropriate more often than widely appreciated. There was strong agreement among participants that placebo-surgery controlled trials are ethically appropriate and even required to answer some questions. They argued that placebo-surgery controlled trials are ethically justifiable and feasible for cellular implants, but not for deep brain stimulation (DBS), for PD.

While participants maintained they have insufficient information to make adequate disclosures about DBS, most agreed that PD patients (without dementia) are well-informed and capable of providing valid consent. The most vulnerable prospective subjects, they agreed, are those who fail to meet eligibility criteria and are poor candidates for DBS for PD. Informed consent for surgical research involving PD is complex, and in the case of DBS, needs to counter unrealistic expectations generated by reports in the media. The participants discussed methods to enhance comprehension and reduce conflation of research with therapy.

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Adaptive Algorithm for 3D Cortical Control of an Anthropomorphic Prosthetic Arm

M. Velliste[1,3], M.C. Spalding[2,3], and A.B. Schwartz[1,2,3]

[1]Department of Neurobiology, University of Pittsburgh, Pittsburgh, PA
[2]Department of Bioengineering, University of Pittsburgh, Pittsburgh, PA
[3]Center for the Neural Basis of Cognition, University of Pittsburgh and Carnegie Mellon University, Pittsburgh, PA

It has been shown that the firing rates of motor cortical cells can be modulated in the absence of real limb movement. Combined with technological advances, this has enabled the creation of motor prosthetic devices that will restore the ability of amputees or paralyzed persons to interact with their physical environment. The activity of motor cortical neurons can be used to control the movements of a prosthetic arm because the cells are broadly tuned with movement direction and fire maximally in a *preferred direction* (PD). Previous experiments in monkeys have shown that the direction and speed of natural hand movement can be predicted from the firing rates of a population of motor cortical cells, and that the entire continuous hand trajectory can be reconstructed from the neural activity. Therefore, this brain area seems a logical choice for deriving the prosthetic control signal, but an accurate estimate of the cells' PDs is required for good control. Considering the motor impairment of the target users of this technology, it must be possible to derive the PDs in the absence of the subjects' own arm movement.

We have created a system for real-time cortical control of an anthropomorphic (human-like) prosthetic arm and a new adaptive method for calibrating the control algorithm while a subject is using the prosthesis. Monkeys control the arm to reach for a food reward presented at one of four targets in 3D space and then retrieve the food to their mouth. The algorithm is initialized with random PDs, then regresses the cells' firing rates with the current target direction, continuing iteratively over multiple trials to different targets, until the preferred direction of each cell stabilizes. The animals start out with no control over the arm, but quickly gain progressively better control, achieving good performance after only 15-20 reach and retrieval movement pairs. We have subsequently used this system in a continuous 3D control task where the arm is under cortical control 100% of the time during an entire session, and a monkey was able to reach, stabilize the arm for loading, and successfully retrieve over 80% of presented targets on most days.

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Electrochemically Controlled Release of Dexamethasone from Conducting Polymer Polypyrrole Coated Electrode

Reecha Wadhwa[1], Carl F. Lagenaur [2], and Xinyan Tracy Cui[1,3]

[1]Department of Bioengineering, University of Pittsburgh, Pittsburgh, PA
[2]Department of Neurobiology, University of Pittsburgh, Pittsburgh, PA
[3]McGowan Institute for Regenerative Medicine, Pittsburgh, PA

Topic area: Materials and Devices

Micromachined neural electrode arrays facilitate the functional stimulation of and recording from the peripheral and central nervous systems. Chronic recordings from these often fail a few weeks after implantation, primarily due to the formation of an astro-glial sheath around the implant. We propose a novel drug-delivery system from conducting polymer (CP) coatings on the electrode sites to modulate the inflammatory implant-host tissue reaction. In this study, polypyrrole (PPy)-based coatings for electrically controlled and local delivery of the ionic form of an anti-inflammatory drug, dexamethasone (Dex), was investigated. The drug was incorporated in PPy via electropolymerization of pyrrole on the anode and released in PBS using cyclic voltammetry (CV). FTIR analysis of the surface showed the presence of Dex and polypyrrole on the coated electrode. The thickness of the coated film was estimated to be ~50 nm by ellipsometry. We are able to release 0.5 $\mu g/cm^2$ Dex in 1 CV cycle and a total of almost 16 $\mu g/cm^2$ Dex after 30 CV cycles. *In vitro* studies and immunocytochemistry on murine glial cells suggest that the released drug lowers the proliferation of reactive astrocytes to the same extent as the added drug. In addition, the released drug is not toxic to neurons as seen by healthy neuronal viability in both control and released drug-treated cells.

We acknowledge the financial support provided by the Whitaker Foundation, Department of Bioengineering (University of Pittsburgh), McGowan Institute of Regenerative Medicine, University of Pittsburgh, Competitive Medical Research Fund and Central Research Development Fund for financial support.

Signal Amplification, Detection, and Transmission in a Wireless 100-Electrode Neural Recording System

Paul T. Watkins[1], Ryan Kier[1], Robert Lovejoy[1], Daniel J. Black[1], Richard Normann[2], Florian Solzbacher[1], and Reid R. Harrison[1,2]

[1]Department of Electrical and Computer Engineering, University of Utah, Salt Lake City, UT
[2]Department of Bioengineering, University of Utah, Salt Lake City, UT

Topic area: Brain Computer Interface

We have developed a single-chip, low-power neural recording system with wireless power delivery and telemetry. The integrated circuit, which was fabricated in a commercial 0.5-_m 3-metal, 2-poly CMOS process, is designed to be flip-chip bonded onto the back of a 100-channel Utah Electrode Array. Twelve of the 100 platinum-tipped electrodes will be used as "ground" or "reference" electrodes; the remaining 88 electrodes will be connected to integrated low-noise neural signal amplifiers. The amplifiers are laid out in a 10 × 10 array at a 400-_m pitch, corresponding to the inter-electrode spacing. A small bond pad local to each amplifier allows connection of the chip to the MEMS electrode array. The complete Integrated Neural Interface (INI) will include a 6-mm diameter coil for wireless power reception and will be encapsulated with SiC and parylene prior to implantation.

The neural signal amplifiers are designed to amplify action potentials ("spikes") and reject local field potentials; each has a gain of 60 dB over a bandwidth from 1 kHz to 5 kHz. A 10-bit charge-redistribution ADC is used to digitize the signal from 1 amplifier selected with an analog MUX. Neural data is digitized at 15,000 samples per second. We also perform data reduction by incorporating one-bit "spike detector" comparators into each amplifier block. The spike detection threshold is set by a DAC, and is programmable. The chip produces a 330-kbps data stream that interleaves the ADC data from a single amplifier, spike detector data from all amplifiers, and parity bits. Digitized neural data is transmitted off-chip using a fully integrated 433-MHz FSK transmitter. The complete chip measures 4.7 mm × 5.9 mm and contains over 30,000 transistors and 5,000 passive components. The targeted total power dissipation is 10 mW to minimize the heating of surrounding tissues.

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A DRG-Based Sensory Neural Interface

D.J. Weber[1,2], R.B. Stein[2], D. Everaert[2], and A. Prochazka[2]

[1]Department of Physical Medicine and Rehabilitation, University of Pittsburgh, Pittsburgh, PA
[2]Centre for Neuroscience, University of Alberta, Edmonton, AB

Sensory feedback is required by biological motor control systems to maintain stability amid perturbations and adapt to system and environmental changes. Similarly, motor neuroprostheses require feedback to provide natural and complete restoration of motor functions. We have found that proprioceptive signals from the body's mechanoreceptors can provide a natural source of kinematic state information that could be useful for prosthetic control. To date, we have implanted a chronic recording array (9x4 grid, Cyberkinetics, LLC) into the L7 dorsal root ganglia (DRG) of five cats. During the first 7-14 days after surgery, we are typically able to simultaneously record from 20-30 neurons, but recordings gradually worsen thereafter. Histology indicates that a ring of inflammatory and connective tissues (100-μm thick) develops around each microelectrode and likely contributes to the degradation in recording quality.

Accurate estimations of hindlimb trajectory during walking are made using a linear filter with inputs from only a few neurons highly correlated with the kinematics. Neurons are selected for decoding based on their correlation with the kinematic variables. The coefficients for the linear filter are identified in a least-squares fit with 5-10 seconds of walking data (model training stage). Separate (nontraining) data are used to test model performance. The estimated and actual trajectories generally match well for walking at a range of speeds. The reconstructions account for 63 ± 22% (average across three joints ± S.D.) of the variance in joint angle and 72 ± 4% of the variance in joint angular velocities. Using endpoint coordinates, the variance accounted for by the reconstruction is 79 ± 5% for position and 74 ± 8% for velocity variables. The largest errors are in orientation angle and angular velocity estimates during the late stance and early swing phases. These results indicate that a neural interface with primary sensory neurons in the dorsal root ganglion can provide accurate kinematic state information that may be useful for closed-loop control of a neuroprosthesis.

This work was supported by the Canadian Institutes of Health and the Alberta Heritage Foundation for Medical Research.

Effect of the Electrode-Electrolyte Interface on the Current Density Distribution on Deep Brain Stimulating Electrodes

Xuefeng F. Wei and Warren M. Grill

Department of Biomedical Engineering, Duke University, Durham, NC

Topic area: Electrodes

The properties of the interface between metallic deep brain stimulating (DBS) electrodes and brain tissue have not been considered in previous models of DBS. We implemented a finite-element model of a monopolar DBS electrode that incorporated a representation of the electrode-tissue interface by inserting an impedance between the metal electrode and the tissue volume. The electrode-tissue interface impedance was represented by the parallel combination of a double-layer capacitance (C_{dl}) and a Faradaic charge-transfer resistance (R_f). Previous results indicate that R_f is a nonlinear function of current density, and we implemented both a lumped model that did not account for the nonlinearity of R_f and a distributed model that approximated the nonlinearity of R_f. Parameters for C_{dl} and R_f were obtained from previous measurements on Pt-Ir electrode in 0.9% NaCl at 25^{o}C. Steady-state solutions of current density distributions along the electrode surface and impedance spectrograms from 1 Hz to 10^5 Hz were generated for both the lumped and distributed models.

The impedance spectrograms for both models had a low-pass filter characteristic with a low-frequency impedance of ~1.2 k_ at 1Hz, a cut-off frequency of ~ 100 Hz, and a high frequency impedance of close to 0 _ at 10^5 Hz. The impedance spectrum was in good agreement with impedance spectra of DBS electrodes measured *in vitro*. The current density distributions along the electrode surface in both the lumped and distributed models were nonuniform and frequency-dependent. The current-density distributions at high frequencies (>1 kHz) were almost identical to the primary current-density distribution obtained from a model without an electrode-tissue interface, and were highly nonuniform with the highest current density at the edges of the contact and the lowest current density in the center of the contact. The nonuniformity of the current density decreased with decreasing frequency, and the current density was more uniform than the primary current density distribution. Further, the distribution of the current density was more uniform in the lumped model and did not exhibit the edge effects at low frequencies (<10 Hz) that were observed in the distributed model.

These results indicated that the impedance of the electrode-electrolyte interface influences the distribution of current density on the electrode surface. The current density on the electrode can influence tissue damage, electrode corrosion, and the patterns of excitation generated in the tissue.

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Optimized Laser Parameters for Safe and Efficient Stimulation of Neural Tissue In Vivo

Jonathon Wells, Duco Jansen, Anita Mahadevan-Jansen, Peter Konrad, and Chris Kao

Departments of Biomedical Engineering and Neurological Surgery, Vanderbilt University, Nashville, TN

Topic area: Sensory/Motor and Functional Neural Stimulation

For nearly two centuries, neural stimulation has been based primarily on electrical methods, in which potentials are initiated with an applied voltage. Neural stimulation is an essential method both in fundamental neurophysiological studies and in a number of clinical applications involving both the peripheral and central nervous systems. While significant advances have been made in electrode design and stimulation approaches since the early days of electrical neural stimulation, the method is fundamentally unchanged and limited. In particular, spatial precision of stimulation is limited due to the size of electrodes and, more importantly, the inherent induction of an electric field spanning a spatial area many times the size of the electrode, resulting in a population response due to the recruitment of multiple axons, and in general, poor spatial specificity. Moreover, stimulation artifacts on the recording electrode continue to frustrate electrophysiologists and prevent electrode recordings immediately adjacent to the point of stimulation. These inherent shortcomings have lead researchers to search for alternative methods for neural stimulation.

Recent work in our laboratories has shown feasibility of a fundamentally different approach to neural stimulation by using optical rather than electrical energy to induce nerve potentials. This approach presents a new paradigm to *in vivo* neural activation based on pulsed infrared light. Optical stimulation provides a contact-free, spatially selective, artifact-free method that may have significant advantages over electrical techniques for numerous diagnostic and therapeutic clinical applications. Results demonstrate that low-level laser energy can be used to consistently and reproducibly stimulate action potentials in discrete populations of peripheral nerves with resulting compound nerve and muscle potentials in frogs and rats *in vivo* with no appreciable tissue damage using radiant exposures well below the damage threshold. Results therein prove that this phenomenon is wavelength-dependent, and the stimulation threshold follows the inverse of soft tissue absorption; thus, stimulation threshold is a function of the penetration depth of light in tissue. An optimal wavelength of 2.12 μm for efficient, safe stimulation is proposed for the rat sciatic nerve. The results described validate that stimulation using a portable Holmium:YAG (2.12 μm) laser with optimized parameters can circumvent limitations of electrical stimulation. In fact, translation of the optical fiber (400-600 μm) can stimulate specific individual motor fascicles within a main peripheral nerve *in vivo*. The strength-response curve associated with this modality mirrors that of electrical stimulation. Ultimately, the goal is to explore the concept of optical stimulation to chronically excite neural potentials *in vivo* geared toward future clinical and research applications to facilitate advancement in neural interfaces and neurotechnology.

We acknowledge the support of the W.M. Keck Foundation Free-Electron Laser Center, as well the MFEL program (Grant FA9550-04-1-0045).

Comparing Quality of Life in Parkinson's Disease in Patients With and Without Deep Brain Stimulation

J.C. Wertheimer[1,2], M. Tuchman[1], C. Walton[1], R. Kramer[1], J. Wherry[1], and L.R. Kingery[1]

[1]The Parkinson Alliance, Kingston, NJ
[2]Department of Neuropsychology, Wayne State University School of Medicine, Detroit, MI

Quality of life (QoL) has been extensively studied in Parkinson's disease (PD), but few large studies assessing QoL in PD patients who have been treated with deep brain stimulation (DBS) have been conducted. The current study summarizes findings of a survey research project that examined QoL in 108 PD patients who underwent DBS of the subthalamic nucleus and 71 PD patients who did not. Survey instruments included the Beck Depression Inventory-II (BD-II), a PD-specific QoL questionnaire, and other questions relevant to health and QoL.

The average ages of the DBS and non-DBS groups were 62 (SD=9.7) and 61 (SD=10.2), respectively, and did not differ significantly. The groups were well-matched in terms of gender (DBS=61% male, non-DBS=54% male) and marital status (DBS=79% married, non-DBS=82% married). The average duration of PD in the DBS group was nearly twice as many years (DBS=15 years, non-DBS=7 years). There were no significant differences between the two groups on the BDI-II, even after controlling for disease duration. Significantly more non-DBS participants reported depression that existed prior to being diagnosed with PD. A smaller proportion of DBS patients was taking antidepressant medications, even though nearly equal proportions in each group reported being diagnosed with depression (DBS=40%, non-DBS=45%). Of those participants taking an antidepressant, DBS participants reported antidepressants as less effective than the non-DBS group.

Essentially equivalent levels of overall satisfaction with health, QoL, and movement disorder symptoms were observed between the two groups, with one exception: speech problems. Irrespective of disease duration, a statistically significant difference between the two groups emerged on self-reported problems with articulation and fluency of speech (the Cohen's d effect size = .77). The relationship between disease duration and satisfaction with overall severity of the movement disorder was correlated in the non-DBS group, but not the DBS group. Depressive symptoms were highly predictive of poor satisfaction with multiple scales of health, social, and movement disorder-related QoL, and high rates of self-reported depression were evidenced in both groups.

With consideration of the methodological limitations of this study, these results contribute uniquely to an emerging body of research whose aim is to document and understand clinically relevant QoL variables in individuals with PD who have or have not undergone DBS. Our future work will include a longitudinal study of this cohort. This research will provide much needed information about the effects of DBS over time.

A Wireless Wearable Controller for an Upper Extremity Neuroprosthesis

Christa Wheeler and P. Hunter Peckham

Department of Biomedical Engineering, Case Western Reserve University,
Cleveland Functional Electrical Stimulation Center, Cleveland, OH

The objective of this project is to develop a wireless, wearable joint-angle transducer to enable proportional control of an upper-extremity neuroprosthesis using wrist position. Implanted neuroprostheses developed at Case Western Reserve University use functional electrical stimulation (FES) to provide hand grasp to individuals with tetraplegia. Muscles under voluntary command are used to proportionally control the degree of hand grasp and opening. Various command sources have been used clinically, including contralateral shoulder movement, wrist position, and myoelectric signals from muscles, with retained voluntary control (Hart et al., 1998). Wrist position is advantageous because it can be used for bilateral control and augments the tenodesis grasp. Recently developed battery-powered implantable stimulators utilize wireless telemetry and can accept RF signals for control. Thus, a wireless and cosmetically acceptable external wrist controller is being developed for command signal acquisition.

The goal of the project is to provide the user with a wearable controller, similar in size to a wristwatch, that will include a sensor to measure joint angle, the conditioning electronics, and an RF transmitter with a small antenna. Based on functional specifications, including cosmesis, precision, size, and cost, a magnetoresistive (MR) angular displacement sensor was chosen for further evaluation. The sensor is composed of four MR elements in a Wheatstone bridge. The resistivity of each element is dependent on the direction, rather than the strength, of an applied magnetic field. This allows for large variations in gap between the sensor and the magnet, ideal for an angle transducer in which the two must be located on opposite sides of the joint. A mechanical model of a hand with a one-degree of freedom joint to mimic wrist flexion and extension was designed for evaluation of the sensor. Preliminary tests using an MR sensor attached to the wrist and a rare-earth, disc-shaped magnet on the top of the hand indicate a distinct relationship between sensor output and wrist position. Future research will consider implantation of the magnet, further improving cosmesis and ease of wear.

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Hart R.L., Kilgore K.L., Peckham P.H. A comparison between control methods for implanted FES hand-grasp systems. *IEEE Trans Rehab Eng*, 6(2):208-218, 1998.

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Use of Cervical EMG Signals as a Command Interface for a High Tetraplegia Neural Prosthesis

Matt Williams and Robert Kirsch

Department of Biomedical Engineering, Case Western Reserve University, Functional Electrical Stimulation Center of Excellence, Cleveland VA Medical Center, Cleveland, OH

Topic area: Neural Prosthesis

A cervical-level spinal cord injury can result in significant loss of function and impact both the injured individual as well as their family and caregivers. Neural prosthetics offer a potential solution to this loss of function, and may enable a greatly enhanced level of self-dependence. With a high-level injury, the amount of function that must be restored is substantial, while the number of voluntary actions available to serve as command inputs is markedly limited. The problem comes down to one of controlling the position and orientation of the hand in space with the remaining voluntary actions that are limited to the head, neck, and face, due to the injury level. Despite the significant loss of many voluntary actions, a number of potential command sources remain by which the user can produce the 3D control signals necessary to restore arm function. One of these actions is voluntary control of the muscles of the neck and shoulder girdle, which control head stabilization and orientation. This study is an investigation of this potential command interface and its applicability as an input to a neural prosthetic for high tetraplegia.

While EMG input for prosthetic applications is a well-developed technology, it's application via cervical EMG to control of a full-arm neuroprosthetic is novel. This technology is attractive as a user interface, as it is easily modulated by a user, able to be obtained using conventional means, and is a mature technology that is readily implantable in the final device.

The muscles used in the study are the sternocleidomastoids, the platysma, and the trapezius. All signal recordings are collected using surface electrodes and processed using a custom controller to evaluate intentional user signals into motion commands for an anthropomorphic robot arm serving as a proxy to a paralyzed arm.

Users were able to generate EMG signals, either singularly or in combinations, that were interpreted into commands for the robot arm. Three degrees of freedom were controlled in this manner to specify arm position. Another two degrees of freedom for control of the forearm and hand were available by switching to a different mode with a "double-click" of the trapezius. Using this system, users were able to move the robot arm around in the workspace that would be available to an individual with a neural prosthesis stimulating a paralyzed arm. This work illustrates the applicability of using EMG signals from the neck as a command source for a full-arm neural prosthesis.

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Design and Implementation of the Electronics for a 96 Channel Implanted Brain-Machine Interface

Patrick D. Wolf [1,2], Miguel A. L. Nicolelis[2,3], Chad A. Bosetti[1,2], Stephen H. Callender[1,2], Michael Rizk[1,2], and Thomas A. Jochum[1,2]

[1]Department of Biomedical Engineering, Duke University, Durham, NC
[2]Center for Neuroengineering, Duke University, Durham, NC
[3]Department of Neurobiology, Duke University, Durham, NC

Successful implementation of a clinical brain-machine interface (BMI) will require an implanted system capable of recording from multiple cortical electrodes simultaneously. We have designed and are building a 96-channel system capable of recording, processing, and wirelessly transmitting spike information from subcutaneous implants to a wearable communications link. The system consists of three electronic modules: (1) a 32-channel digitizing headstage module (DHSM), (2) an implanted central communications module (ICCM), and (3) a wearable communications module (WCM). The 96-channel system includes 3 DHSMs, an ICCM, and a WCM. The DHSM is made from two identical 16-channel, custom neural amplifier integrated circuits, an A/D converter, and a logic IC (CPLD). The headstages amplify, filter (300-5,000 Hz), time multiplex, and digitize (31.25 kHz) the 32 neural signals. The modules measure approximately 43x7x7 mm and weigh less than 5 grams. These modules will be implanted subcutaneously on the bone adjacent to a craniotomy. They will connect via subcutaneous cables to the ICCM, which will be implanted in the pectoral or scapular region.

The ICCM is functionally divided into three sections: (1) power conversion and distribution, (2) data reception and processing, and (3) telemetry. The ICCM provides the power for all the implanted modules via a transcutaneous power link with the WCM. RF energy (250 kHz) is received on an implanted coil, rectified, and regulated to supply power to all of the implanted devices (≈2 Watts). The raw data from three headstages (36 Mbits/sec) is received and processed by an FPGA to produce a data stream for transmission to the WCM. The output data types include: raw signals from individual channels, detected spike waveforms, and 1-mS bin counts of detected spikes. Detection is implemented as automated equal positive and negative thresholds. The telemetry is implemented using a commercial (RFM) AM (916.5 MHz) transceiver with a raw data bandwidth of 1 Mbit/sec. All encoding and decoding is done in the FPGA. The resulting net data transfer rate is approximately 0.8 Mbit/sec. The implanted transceiver receives commands from the WCM and sends back neural data and system control information. The WCM receives and decodes the data transmissions from the ICCM and formats them for retransmission to a computer. A user interface is used to view the data and issue commands to the implanted modules by way of the WCM. The WCM also produces RF energy for the transcutaneous power transfer by switching a 24-volt DC power input. The WCM will be worn or stationed near the subject. The power coil, however, must be maintained within 2 cm of the implanted coil.

The wireless power and data transmission features of this BMI make it suitable for long-term use without the risk of infection from percutaneous connectors. This BMI system has been prototyped and is being implemented with a near-term goal of animal testing.

This work is supported by DARPA.

Mapping Neural-Ensemble Activity of Rat Spinal Locomotor Centers During Midbrain-Stimulated Stepping

C.T. Yang[1,2], A. Urdaneta[1], R.R. Roy[3,4], H. Zhong[3], V.R. Edgerton[1,3,4], and J.W. Judy[1,4,5]

[1]Biomedical Engineering Interdepartmental Program, University of California, Los Angeles, CA
[2]David Geffen School of Medicine, University of California, Los Angeles, CA
[3]Department of Physiological Science, University of California, Los Angeles, CA
[4]Brain Research Institute, University of California, Los Angeles, CA
[5]Department of Electrical Engineering, University of California, Los Angeles, CA

Topic area: Mapping or Sensory/Motor and Functional Neural Stimulation

In most spinal-cord-injured patients, lesions rostral to the lumbar enlargement inhibit descending commands from reaching locomotor networks in the lumbar spinal cord. Activation of the interneuronal circuits in the lumbar spinal cord directly via intraspinal microelectrodes has been suggested as an elegant approach for restoring locomotion. Targeting the interneurons in the lumbar cord that may be involved in central-pattern generation could provide coordination and activation of motoneuronal pools with natural recruitment of muscle fibers. Intraspinal stimulation may also aid in recovery through activation of local circuits and potentiation of neurotrophic factors. But the lumbar circuits that make up the central pattern generator are poorly understood. Some of the neurons active during stepping have been identified and many researchers are looking at the role these neurons play. Nevertheless, the fine spatiotemporal sequence in which these neurons are activated within a step cycle has not been mapped during stepping in the rat or in higher animal models. It is likely that several sites need to be activated simultaneously or in sequence and that the effect of stimulating these neurons is state-dependent.

Locomotion was studied in acute decerebrate rats by stimulation of the mesencephalic locomotor region (MLR) to induce stepping. We recorded the neural ensemble activity of an array of sites in regions shown to be important for locomotor-rhythm generation using 80-channel multielectrode arrays implanted in the spinal cord. By mapping the extracellular spike activity and local field potentials in this region, and correlating the activity with electromyographic (EMG) recordings from the ankle extensors and flexors, we identified regions of activation that may be crucial to the initiation or maintenance of stepping. Spatiotemporal population maps were generated from the recorded step cycles to visualize the temporal changes that occured. Using principal-component analysis and independent-component analysis, we characterized the overall neural activity and identified regions that are highly correlated with specific phases of the step cycle or rate of stepping. Anatomical locations of the recorded sites were determined by cresyl violet staining and DAPI and HSP-27 immunolabeling. These results will shed light on the organization of locomotor pattern-generating circuits and identify active regions for stimulation. In future studies, we will test patterned electrical stimulation of the identified hot spots in spinal-cord-transected rats. These efforts will be directed towards the development of a functional stimulator for locomotion in paralyzed patients.

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Minimally-Invasive Peripheral Nerve Stimulation using a Needle Electrode

Paul B. Yoo and Warren M. Grill
Department of Biomedical Engineering, Duke University, Durham, NC
Sensory-Motor and Functional Electrical Stimulation

The clinical translation of novel functional electrical stimulation (FES) technology requires minimally or non-invasive methods to test techniques in human. We have shown that stimulation of pudendal nerve afferents evokes bladder contractions in cats, but evidence of therapeutic efficacy in human subjects is lacking. This study was undertaken to test the hypothesis that bladder contractions can be evoked with a needle electrode using high-frequency stimulation.

The bladder pressures and external anal sphincter (EAS) responses evoked by stimulation of the pudendal nerve were measured in adult cats anesthetizes with alpha-chloralose. A monopolar needle electrode was inserted at five positions along the feline pudendal canal: initially 1 cm rostral to the anus and subsequently at 0.5 cm intervals in the rostral direction. Both low and high frequency cathodic pulses were delivered to locate the pudendal nerve (i.e., minimum electrode-to-nerve distance) and to elicit reflexive bladder contractions, respectively. At each electrode position, stimulation was also applied at successively larger distances (0.5 cm intervals) from the nerve along the path of insertion.

The feline pudendal nerve was accessible over a 1.5 cm segment along the pudendal canal (electrode positions 1 to 4). Close proximity to the nerve was achieved with the needle electrode, as indicated by the average threshold for EAS activity of 0.35 ± 0.09 mA. Sustained bladder contractions using high frequency (33 Hz) trains were also evoked at these electrode positions. The thresholds for eliciting bladder contractions at electrode positions 3 & 4 were similar to those for generating EAS activity: 0.57 ± 0.06 mA and 0.58 ± 0.1 mA, respectively. Furthermore, the mean amplitude of the evoked bladder pressures (19.6 ± 3.0 cmH_2O) was comparable to that obtained with direct pudendal nerve stimulation using hook electrodes.

The needle electrode provides a minimally invasive method to activate the pudendal nerve. This will enable study of reflexes medicated by pudendal afferents in humans, and allow pre-operative testing before implanting a permanent device.

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An Inductively Powered Multi-Channel Wireless Implantable Neural Recording System

Ming Yin and Maysam Ghovanloo

Department of Electrical and Computer Engineering, North Carolina State University, Raleigh, NC

Wireless recording of the neural signals from a large number of recording sites is highly desired because a growing number of neuroscientists have become interested in visualizing the extracellular activities of hundreds to thousands of single neurons in awake, freely moving animals. High site-count neural recording systems are currently hardwired and the tethering effects of the wires attached to implanted electrodes interfere with natural animal behavior and bias the overall results. Considering that neural signals have a bandwidth of about 10 kHz, a wideband telemetry link in the order of tens of MHz is needed to wirelessly record from a large number of sites, simultaneously. So far, most of the reported wireless neural recording systems have been battery-powered, and therefore, not fully implantable except for a short period of time. The objective of the present research is to develop an inductively powered 15-channel wireless implantable neural recording (WINeR) system for long-term *in vivo* experiments. The electrical connection to the neural tissue is formed through either a group of metal microwire electrodes or a micromachined silicon microelectrode array. For every recording channel, a low-noise, low-power amplifier (LNA), which is capable of amplifying signals from milliHertz to kiloHertz range, is used to amplify the acquired neural signals. A capacitive high-pass filter at the input of every LNA rejects the large DC offset generated at the electrode-tissue interface, but not low-frequency-evoked potentials that may contain significant physiologic information. Fifteen identical neural recording channels plus a constant reference voltage (MARK) that marks the beginning of each frame are time-division multiplexed (TDM) by a 16 to 1 multiplexer that is controlled by a 4-bit counter. The counter is run at 320 kHz by a local ring oscillator, taking 20-k samples/second from every channel. This sampling rate should be enough for reconstruction of the neural signals, which have a bandwidth of 8~10 kHz. A sample-and-hold (S&H) circuit follows the TDM to stabilize the acquired samples before pulse width modulation (PWM). The PWM is dedicated to convert the analog signal at the output of the S&H to a pseudo-digital signal that is more robust against noise. Using a pulse-width modulator instead of an analog-to-digital converter (ADC) results in less power consumption and less complexity in the implantable device. A voltage-controlled oscillator (VCO) converts the PWM signal to a frequency shift keyed (FSK) carrier in the industrial, scientific, and medical (ISM) band. Due to the short-range application of the WINeR system (within the animal cage), the VCO output can be directly applied to a miniature patch antenna with a proper off-chip matching circuit. A commercial ISM-band receiver will be used as the external part of the system. The received PWM signal will be directly converted to digitized samples using a high-frequency counter on a PC data-acquisition card. Finally, by demultiplexing the TDM samples, the original neural signals are reconstructed. The WINeR implant also contains a receiver coil, followed by an on-chip rectifier, filter, and regulator that provide the rest of the implant with a clean DC supply. The power carrier frequency is selected to have minimum interference with the neural signals and ISM carrier. The WINeR system has been implemented in the AMI 0.5-_m process and submitted for fabrication.

This work is supported by startup funds provided by the Department of Electrical and Computer Engineering, North Carolina State University.

Parallel Synthesis of Biomaterials for Neural Engineering Using Microfluidics

Xiang Yu and David A. LaVan

Department of Mechanical Engineering, Yale University, New Haven, CT

Materials used for neural interfaces can have problems with stability, biocompatibility, and cell attachment. Conductive polymers have been suggested as candidate materials to coat neural interfaces, as they are conductive and offer easy preparation and modification to their physical, chemical, and/or biological properties. However, there are many choices among monomers and dopants (considering small molecules, growth factors, drugs, etc.) and the choice of the optimal composition is not obvious.

We have developed a microfluidic-based parallel synthesis reactor to automate the creation and evaluation of poly(Pyrrole)-based biopolymers. A prototype that is capable of synthesizing and screening over 100 compositions on a chip has been tested. Recent work has started to scale it up, using devices based on immiscible liquid plugs. Four aqueous streams of monomers or dopants meet and form one stream right before intersecting a stream of an immiscible liquid. Plugs can be generated by shearing the aqueous stream into a stream of oil inside microchannels[1-3]. Computer-controlled pumps control the composition of the liquid within each plug. Mixing of reagents within plugs is achieved by passing plugs through a long series of meanders.

The plugs are trapped by surface tension into micro-wells that have larger exposed surface areas than the channel[4]. Subsequent plugs flowing down the channel will skip those wells already occupied; the coalescence of plugs is suppressed by surfactant intentionally added in the oil and by adjusting plug spacing. A microarray is generated by filling all the wells. Polymerization occurs by electro-oxidation of the mixtures of monomers and dopants with charge applied using microelectrodes lithographically patterned underneath each well. Lastly, the microfluidic device is removed from the test surface, leaving an array of polymers for *in vitro* analysis.

The system currently produces features of ~50 micrometers. The goal of the project is to evaluate a library of 10^5 polymer combinations using subsequent generations of the device.

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Microelectrode Array Recording and Correlation of Respiratory Neuronal Activities in Pontine Local Neural Networks

Yun-Guo Yu, Gang Song, Shawna MacDonald, and Chi-Sang Poon

Harvard-MIT Division of Health Sciences and Technology, Massachusetts Institute of Technology, Cambridge, MA

Topic area: Electrodes (Chronic Recording Microelectrode Array)

The pneumotaxic center in the dorsolateral pons is of critical importance in maintaining normal eupneic breathing pattern. Recently, studies in this laboratory revealed unique time-dependent gating, activity-dependent learning, and memory mechanisms in pontine processing of inputs from peripheral chemoreceptors and pulmonary mechanical receptors, which are feedback signals controlling respiratory rate and tidal volume. To delineate the pontine neuronal networks underlying these pneumotaxic functions, we employed a Multichannel Acquisition Processor (Plexon, Inc.) with an extracellular microelectrode array (Micro Probe, Inc.) to record from multiple dorsolateral pontine neurons simultaneously and to analyze their responses to brief hypoxia (8% Oxygen, 20 seconds) or vagal electrical stimulation (80 Hz, 20-40 _A, 1 minute). Experiments were performed on urethane-anesthetized, bi-vagotamized, paralyzed, and artificially ventilated adult rats. Of a total of 339 dorsolateral pontine neurons recorded, 154 (45%) were found to be modulated by either vagal stimulation or hypoxia. Among them, 93 units (27%) were found by cross-correlation analysis to exhibit respiratory rhythmic modulations (phasic activity synchronized to respiratory rhythm). Most respiratory-modulated neurons were tonically discharging with superimposed inspiratory, expiratory, or phase-spanning discharge patterns. In addition, 41 (12%) normally quiescent neurons were recruited into firing either by hypoxia and/or vagal stimulation, suggesting that afferent inputs from peripheral chemoreceptors and pulmonary stretch receptors can recruit and synchronize pontine neurons into rhythmic activity. Presumably, vagal stimulation and/or hypoxia may disinhibit rhythmic activity that propagates in a functionally interconnected network. Such synchronization and recruitment properties have important implications in respiratory frequency control and spatio-temporal patterning in respiratory neuronal networks, and in the putative-gating mechanism in respiratory control. Further cross-correlation analysis is currently underway to systematically delineate the interconnections among these pontine neurons, and to discern the neural correlates of the gating mechanism in the pontine respiratory neural network. The latter will be achieved by the demonstration of time-dependent changes in the interconnectivity and interactions of respiratory neurons in the "pneumotaxic" dorsolateral pontine region. Mapping the local neuronal circuits in this pontine structure will increase our understanding of how pneumotaxic neurons process respiratory-related information in a gated manner to produce phase-dependent learning.

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Highly Compliant Electrode Arrays for Improved Modulus Matching

Zhe Yu[1], Stéphanie P. Lacour[2], Candice Tsay[2], Sigurd Wagner[2], and Barclay Morrison, III[1]

[1]Department of Biomedical Engineering, Columbia University, New York, NY
[2]Department of Electrical Engineering, Princeton University, Princeton, NJ

Topic area: Materials and Devices

Implantable microelectrode arrays (MEAs) offer the promise of interfacing the brain with electronic devices to restore lost functions or treat neurological diseases. However, due to the large modulus mismatch between rigid metal MEAs (Young's modulus ~ 100 GPa) and brain tissue (Young's modulus ~ 10 kPa), irreversible tissue damage often occurs due to micro-motion. Avenues are being pursued to develop soft and flexible substrates for MEAs using bendable foils as substrates. Flexible MEAs have been produced on polyimide (Young's modulus ~ 5 GPa), although it is much stiffer than brain. The use of flexible substrates is limited by the performance of the patterned metals, as polyimide electrodes fail if bent or flexed greater than 1-2% strain.

We have fabricated a much more compliant MEA consisting of patterned gold electrodes on polydimethylsiloxane (PDMS, Young's modulus 1~ 5 MPa). Metallic conductive layers (5 nm Cr/25 nm Au/5 nm Cr) are prepared on the PDMS substrate by electron beam evaporation. Electrodes can be patterned into any shape with a shadow mask with features as small as 100 μm. The electrode pattern is then encapsulated and insulated with a 15-_m thick, photo-patternable silicone (WL-5150, Dow Corning) spun on top of the electrodes. Vias are opened in the insulating layer by photolithography to expose recording/stimulating sites.

We have found that these electrodes are very robust mechanically. They are able to withstand stretching up to 100% without loss of conduction. Electrode resistance in the unstretched configuration is approximately 500 Ω, which increases to approximately 10 kΩ when stretched. This range of impedances is negligible compared to the input impedance of microelectrodes immersed in a physiological solution (generally about 100 kΩ ~ 2 MΩ). *In vitro* biocompatibility testing with organotypic brain slice cultures indicates that the fabrication process and the electrodes are not toxic as slices appeared healthy after 7 days *in vitro*. An *in vitro*, stretchable microelectrode array (SMEA) with 16 channels is being developed to test the recording and stimulating capabilities of the SMEAs.

If the development of the SMEA is successful, this stretchable electrode technology could find application in a wide variety of uses, including conformal surface electrodes for brain recording; stretchable and conformal electrodes for restoration of organ function (e.g., bladder control); and robust interfaces to dynamic tissues, such as muscles. A better modulus match with the organ tissue should reduce chronic damage from micro-motion and maintain a low-impedance interface without scar formation.

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Effects of RNAi-Mediated PSD-95 Suppression on Developing Neurons: A Microfluidic Approach

Henry C. Zeringue and Martha Constantine-Paton

Departments of Biology and Brain and Cognitive Science and the McGovern Institute for Brain Research, Massachusetts Institute of Technology, Cambridge, MA

Topic: Microfluidics (Second Choice: Materials and Devices)

The synapse is the major cellular-level facilitator of communication within the nervous system. Strengthening and loss of the synapse helps form effective network pathways for the transmission of information. Information passes from the presynaptic cell to the postsynaptic cell where it encounters a protein-dense region at the postsynaptic membrane known as the postsynaptic density (PSD). The PSD is critical for synapse formation in the developing CNS, and the signaling properties of an individual PSD help to determine the activity-dependent characteristics that influence synaptogenesis. Glutamate, the major excitatory transmitter in the CNS, transduces through the glutamate family of synaptic receptors. PSD-95, a scaffolding molecule associated with various types of glutamate receptors, is central to the signaling properties of the PSD in developing synapses. Although this protein is instrumental in long-term synaptic potentiation, the range of PSD-95's functions at the developing synapse is poorly understood.

We are using RNA interference (RNAi) to suppress the production of PSD-95 during the maturation of visual system neurons. Viral vector delivery allows the acute introduction of small inhibitory RNA (siRNA) against PSD-95. We have developed a lentiviral vector to deliver the siRNA coding regions as well as the enhanced green fluorescent protein (eGFP) reporter to visual neurons. Four different PSD-95 siRNAs plus four scrambled control sequences are being used to explore efficacy and specificity of PSD-95 suppression. We have fabricated a microfluidic flow chamber to deliver the virus to *in vitro* neuron cultures. Microfluidic laminar flow streams are being used to present the viral vector as well as other pharmacological agents to distinct substrate regions.

Cultures of primary visual cortical (VC) neurons are used to explore the effects of PSD-95 suppression on development of synaptic connections and arborization. We are using microfluidic flow chambers molded into poly(dimethyl siloxane) (PDMS) to expose discrete regions of a developing neuron field to distinct flow streams. One flow stream contains the viral agent while other streams may contain one or more pharmacological agents. By utilizing adjacent flow streams, we are able to explore the changes in synaptic development between as well as within regions. Using three flow streams allows us to examine differing interactions when either side of the viral-infected field is exposed to distinct pharmacological stimuli. This technique yields another modality to explore the function of PSD-95 in synaptic development at the cellular and molecular levels.

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In Vitro *Study of the Anti-Inflammatory Effects of Dexamethasone for Cortical Neural Prosthetics*

Yinghui Zhong and Ravi V. Bellamkonda

Neurological Biomaterials and Therapeutics, Wallace H. Coulter Department of Biomedical Engineering, Georgia Institute of Technology/Emory University, Atlanta, GA

Topic area: Neural Prosthesis

Long-term performance of chronically implanted neural microelectrodes is compromised by glial scar formation around the Si-microelectrodes and subsequent fibrotic encapsulation of the electrode. Glial scar is a consequence of inflammatory reaction to the implant-associated injury to the CNS. One strategy to enhance the performance of implanted electrodes is to develop biocompatible electrode coatings that locally release anti-inflammatory drugs. Dexamethasone (DM) is commonly used in the CNS for its anti-inflammatory effects and its ability to close the damaged blood-brain barrier. The objective of this research is to gain an understanding of dexamethasone's effects on microglia, astrocytes, and neurons *in vitro*.

The initial response to CNS injury is mediated by microglia. NO produced by expression of inducible nitric oxide synthase (iNOS) in microglia is an important mediator of inflammation and neuronal cell death. Therefore, the capacity of DM to inhibit NO production by lipopolysaccharide (LPS)-stimulated primary microglia was evaluated. The results showed that 100, 10, and 1 _M DM inhibited NO production 90%, 98%, and 91%, respectively. In addition, DM treatment at all three concentrations significantly reduced LPS-stimulated microglia proliferation.

Astrocytes are a major cell component in glial scar. When primary mature astrocytes were treated with 100, 10, or 1 _M DM for 7 days, the cell number was significantly reduced compared with the control group. Live/dead assay showed that the survival rate for DM-treated astrocytes was more than 99%, indicating that DM inhibits astrocyte proliferation. While the release rate of DM from polymer coatings can be controlled *in vitro*, the precise *in vivo* dosage is hard to estimate. To evaluate the safety of variations in DM dosing, we explored the effects of DM on cortical cells at 1, 10, and 100 _M (1 _M is the normal target dosage). When rat cortical neurons were incubated with 100, 10, or 1 _M DM, all three concentrations of DM did not significantly alter cell number compared with the control group, indicating that DM was not neurotoxic.

In conclusion, DM is able to inhibit NO production by activated microglia, inhibit microglia and astrocyte proliferation, and is not neurotoxic even at 100 times its normal treatment dosage. This study gives some insight into the mechanism by which DM mediates its anti-inflammatory effects in neural tissue, and confirms that local delivery of DM has the potential to reduce the inflammation at the electrode-brain interface to facilitate long-term recording and stimulation from cortical neural prosthetics *in vivo*.

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