Comparing Auditory Middle Latency Response Using Disc, Bipolar, and Tripolar Concentric-Ring Electrodes

Rushi Acharya and W. Besio

Department of Biomedical Engineering, Louisiana Tech University, Ruston, LA

Rationale: Auditory-evoked and movement-related potentials are signals commonly used in the diagnosis of neurological disorders. We compared the auditory middle-latency response (AMLR) recorded from disc, bipolar, and tripolar concentric-ring electrodes and different locations.

Methodology: Ten healthy volunteers sat relaxed with their eyes closed and were given 33 audio cues per minute. Conventional-disc as well as bipolar and tripolar concentric-ring electrodes were used to record AMLR. Three 1.0-cm diameter electrodes were used to record from the scalp and a single 1.0-cm diameter electrode was used on the ipsilateral mastoid process. The scalp electrodes were placed in a line 2.0 cm apart. For comparison, all recordings were from the same locations, and virtual-disc and bipolar concentric-ring electrodes were fashioned from the tripolar concentric-ring electrodes. Virtual-disc electrodes were created with all rings of tripolar concentric-ring electrodes shorted. Similarly, bipolar concentric-ring electrodes were created using the disc and outer ring of the tripolar concentric-ring electrodes. Two sets of positions on the scalp were selected for recording with the three scalp electrodes, (1) the center electrode located at "Cz" (vertex) and (2) the center electrode located at "C3," with an electrode distal 2.0 cm and another proximal 2.0 cm. Recording was performed in six different sets back to back: (1) disc at Cz and ipsilateral mastoid process, (2) bipolar at Cz and ipsilateral mastoid process, (3) tripolar at Cz and ipsilateral mastoid process, (4) disc at C3 and ipsilateral mastoid process, (5) bipolar at C3 and ipsilateral mastoid process, and (6) tripolar at C3 and ipsilateral mastoid process.

Results/Discussion: When a tripolar concentric-ring electrode was used to record signals over the ipsilateral mastoid process and disc electrodes were used to record from the CZ line, the AMLR present from the disc electrodes was time-aligned with the signal from the tripolar concentric-ring electrode. When the tripolar concentric-ring electrodes were used for recording, there was always a prominent positive and negative peak present from the ipsilateral mastoid process, Cz line, and C3 line locations. A similar time-aligned signal (but with lower amplitude) was present at all locations recorded with the bipolar concentric-ring electrodes as well. When the disc electrodes were used for recording, the AMLR was only present at the Cz line. This leads us to believe that tripolar and bipolar concentric-ring electrodes can record AMLR from the scalp and from the ipsilateral mastoid process. This finding may decrease preparation time and improve signal quality when recording AMLR to help in the diagnosis of neurological disorders.

An I*n Vitro* Model of a Retinal Prosthesis

Ashish K. Ahuja (1), Matthew R. Behrend (1), Masako Kuroda (2), James D. Weiland (2,3)

1. Dept. of Electrical Engineering, University of Southern California, Los Angeles, Ca
2. Doheny Eye Institute, Dept. of Ophthalmology, Keck School of Medicine, University of Southen California, Los Angeles, Ca
3. Dept. of Biomedical Engineering, University of Southern California, Los Angeles, Ca

In order to investigate which elements are excited using an epi-retinal prosthesis under various stimulation protocols, we have designed and fabricated two different multielectrode arrays that mimic the pitch and stimulating electrode sizes that will be used in near-term implants. These arrays comprise 200 and 75 µm roughened Pt stimulating electrodes with 10 and 8 µm stimulating/recording electrodes, respectively. The later are designed to pick up single-unit activity from ganglion cells, and are arranged in radially symmetric manner with respect to the stimulating pads.

Results obtained from isolated retina experiments in the salamander (n=10) indicate that ganglion cells in between 200 µm diameter stimulating electrodes with 500 µm center-to-center spacing can be excited at charge densities as low as 13 $\mu C/cm^2$ for monopolar stimulation and 10 $\mu C/cm^2$ for bipolar stimulation, well below electrochemical safe charge injection limits for Pt (0.35 mC/ cm^2). Surprisingly, introducing twice as much charge into the extracellular space by simultaneously stimulating two adjacent electrodes does not decrease the charge required per electrode in order to elicit a response. This effect is supported using an electrostatic finite-element model to simulate the electric field distribution.

$CdCl_2$ (Ca channel blocker), CNQX (antagonist to AMPA/KAR), APV (competitive antagonist to NMDAR), and PDA (agonist to NMDAR) have been used to show that direct stimulation of ganglion cells has a latency <5ms with respect to stimulus pulse. These blocking agents showed that neural activity with a latency of >5ms is driven presynaptically. When stimulation pulse frequency is increased to approximately 10 Hz ± 4.67Hz, all excitation via presynaptic stimulation mechanism is suppressed regardless of pulse amplitude.

Stimulation of the same ganglion cell (n=4) with both 200 µm and 10 µm diameter electrodes yielded threshold charge densities of 0.012 mC/cm^2 (average cell-electrode edge distance of 87.5 µm) and 7.66 mC/cm^2 (average cell-electrode edge distance of 68.8 µm), respectively. The average absolute charge required, however, was 12.5 nC for the 200 µm diameter electrode and 19 nC for the 10 µm diameter electrode, indicating that a threshold amount of charge must be injected into the extracellular space to elicit a response.

Automatic Control of Standing Balance with Functional Neuromuscular Stimulation – A Dynamic Computer Simulation Study

Musa L. Audu, Raviraj Nataraj, Robert F. Kirsch and Ronald J. Triolo
Department of Biomedical Engineering and Orthopedics, Case Western Reserve University, Cleveland and VA FES Center of Excellence, Cleveland, Ohio, U.S.A.

Functional neuromuscular stimulation (FNS) can provide individuals paralyzed by thoracic or low cervical spinal cord injuries (SCI) with the ability to perform many activities that were previously difficult or impossible from the wheelchair. Experiments have indicated that FNS can readily generate the muscle forces required to rise from a chair and assume a standing posture with minimal assistance from the upper extremities. The major challenge in designing FNS standing systems, however, is to produce timely postural corrections necessary for maintaining dynamic balance in the presence of destabilizing disturbances such as intrinsic motions and unanticipated extrinsic perturbations. Sustaining the required forces for a prolonged period of time in the face of muscular fatigue compounds the challenge. It is unlikely trial-and-error approaches, such as clinical implementation and testing of various control systems, will lead to a successful solution to this problem. A comprehensive biomechanical model and systematic analysis is needed to understand the basic mechanisms that govern standing postural control and to design controllers for FNS-assisted standing.

Using a comprehensive musculoskeletal model, we are investigating control strategies that will use an artificial neural network (ANN) to estimate the muscle excitations required to restore the body to a desired posture from any other posture. To train such an ANN dynamically, data is required on typical excitations required to restore the body from a wide variety of anticipated postures. The method described in this poster is used to generate such data.

Dynamic computer simulation was used to determine histories of muscle excitations required to restore balance from a variety of initial postures that are far away from the erect posture. These postures are lean forward, crouch, lean to the right and lean to the left. The four movements capture the main postures in the three dimensional planes – sagittal, coronal and frontal.

The results of the simulation show that the number of muscles required to restore balance from the four postures was within the number that can be stimulated using 16-channel FES systems if a few muscles are stimulated as a group. In addition to that, the results show that there exists muscle synergies that can be utilized to minimize the number of control variables required to maintain stable balance in subjects with spinal cord injury using the FES systems developed in our laboratory.

Biocompatibility of Silicon, Sapphire and Other Materials Suitable for Neural Implants

Gregory W. Auner[1], K. Y. Simon Ng[2], Ronald Baird[1], Anfeng Wang[1], Paul G. Finlayson[3], Jie Li[4], Kelley Brabant[4], Claudine Jaboro[1], Carolyn A. Black[2,4], Ting Cao[2], Haiying Tang[2], Xuemei Liang[2], Steven O. Salley[2], Golam Newaz[5], and J. P. (Pat) McAllister II[4]

[1] *Department of Electrical and Computer Engineering and Smart Sensors and Integrated Microsystems (SSIM) Program, Wayne State University, Detroit, MI*
[2] *Department of Chemical Engineering and Materials Science, Wayne State University, Detroit, MI*
[3] *Department of Otolaryngology, Wayne State University School of Medicine, Detroit, MI*
[4] *Department of Neurological Surgery, Wayne State University School of Medicine, Detroit, MI*
[5] *Department of Mechanical Engineering, Wayne State University, Detroit, MI*

A wide variety of materials have been used in the development of neural prostheses but the long-term neurocompatibility of many of these materials is unclear. We investigated the short- and long-term biocompatibility and stability in the brain of silicon, sapphire, aluminum nitride, platinum, and borosilicate glass. Wafers (2.5mm dia x 0.25mm thick) of these materials were surgically implanted on the cortical surface of adult rat brain for 10, 28 and 90 days. This study addressed whether the implanted alien materials would cause: (1) deformation of the brain, (2) inflammatory response in the meninges and underlying tissue, and (3) degeneration of the cortical neurons or their efferent and afferent connections. Silicon and sapphire were neither biocompatible nor biostable, causing significantly elevated glial cell reactions in all groups (10-, 28- and 90-day), compared with borosilicate glass, aluminum nitride and sham control. Sapphire also caused significant neuron and axon degeneration. The surface of silicon was noticeably corroded while implanted *in vivo* at all survival periods. In order to prevent these reactions, the surface of silicon wafers was modified by depositing a self-assembled monolayer of **o**ctadecyltrichlorosilane (OTS) or trichloro (3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl) silane (FAS), and two biopolymers (heparin and hyaluronan) were covalently attached to silicon surface with OTS SAM as the bridging layer by UV-based photo-immobilization. This process improved the biocompatibility of implanted sapphire wafers and the *in vitro* biocompatibility of silicon, but the *in vivo* biocompatibility of silicon was only negligibly enhanced. The failure of improvement in biocompatibility was attributed to the poor stability of the surface-modified silicon. *In vitro* stability test with saline solution at 37 °C showed that all the coatings are very stable for up to 30 days, however the harsher physiological environment removed most of the coatings within 28 days. All the coatings on silicon surface were absent after 90 days. AFM analysis of extracted silicon wafers showed pits due to corrosion regardless of the implantation time and type of coating. Therefore, the SAM coatings and heparin/hyaluronan coatings (of only a few nanometers in thickness) failed to protect silicon against corrosion under physiological conditions. If silicon is to be suitable for implantable medical devices, other effective protective and biocompatible coatings must be developed.

Improving the Biocompatibility of Neural Probes by Surface Immobilization of L1

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

Failure of chronically implanted silicon based neural electrode arrays is a major obstacle impeding the development of neural prostheses since their clinical applications will require a life-time-long stable performance. Surface modification of the silicon based neural probes is needed in order to improve their biocompatibility and integration within the host brain tissue.

L1, a neuron adhesion molecule expressed in developing CNS and PNS, is known to promote neurite extension and neuronal survival. We specifically chose this biomolecules based in its unique properties. As positive control we use laminin, a multifunctional extracellular matrix protein that interacts with a variety of cell types, and is also known to be a good substrate for neuronal attachment and growth. The biomolecules are immobilized on silicon dioxide coated wafers using silane chemistry and the coupling agent, 4-Maleimidobutyric acid N-hydroxysuccinimide ester (GMBS). After immobilizing the biomolecules, polyethylene glycol (PEG)-NH_2 was used to inactivate the reactive GMBS and to inhibit non-specific protein or cell-surface interactions. Primary rat cortical neurons and astrocytes were plated on the modified surfaces. Both L1 and laminin promoted neuronal growth, with the L1/PEG immobilized surfaces showing a significantly better neurite outgrowth than the laminin/PEG immobilized surfaces ($p<0.05$). In the astrocyte culture, laminin/PEG immobilized, PEG immobilized, and unmodified silicon surfaces promoted astrocyte growth, while L1/PEG immobilized surfaces were not permissive to astrocyte growth ($p<0.01$). Based on the *in vitro* results, L1 is a better candidate for promoting specific neuronal ingrowth to the neural implant, while minimizing attachment of astrocytes.

Chronic 4-shank Michigan probes were used for the *in vivo* studies. After immobilization of the L1 biomolecule, the probes were implanted in the left and right cortex of mature rats, with laminin/PEG, PEG immobilized, and unmodified probes as controls. After 1 or 4 weeks the rats' brains were sectioned, immunofluorescently stained, and analyzed for neurons, astrocytes, and microglia around the probe insertion site. Reactivity around the implant site was quantified using integrated gray pixel intensity of confocal fluorescence images. After 1 and 4 weeks, the stained tissue sections for the L1/PEG modified probe showed a significant increase ($p<0.01$) of neurofilament activity when compared to unmodified and PEG immobilized probes. Astrocyte reaction in L1/PEG probe tracts was significantly lower than tract reaction analysis of unmodified probe, laminin/PEG, and PEG immobilized probes ($p<0.05$). However, microglia activity was not significant for all conditions.

The result 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.

In vitro and *In vivo* Evaluation of Neural Stem Cells Seeded on Neural Probes

Erdrin Azemi, ***Katelyn Lesk, William R. Stauffer, Glenn Gobbel, X. Tracy Cui***

Silicon based neural electrode arrays are known to experience failure in chronic recording partly due to biocompatibility issues. We propose a surface modification method, by seeding adult neural stem cells (NSCs) on the surface of the probe and we hypothesize that this stem cell layer will act as a biological glue to integrate the device within the brain tissue both structurally and functionally.

In vitro experiments: The silicon surface of the neural probes is not prone to NSC attachment. In order to improve the adhesion of NSCs, laminin was covalently immobilized on silicon dioxide samples. The GFP labeled NSCs, isolated from the subventricular zone of rat brains, were seeded in growth media (GM) or in differentiation media (DM). The NSC-seeded samples were incubated for a period of 3, 7, or 14 days. To evaluate the growth and adhesion of cells, a shear force was applied using an orbital shaker. To assess NSC differentiation, the DM samples were stained for neurons, astrocytes, oligodendrocytes, and neural stem/progenitor cell marker (nestin) after different time points.

In vivo experiments: Laminin immobilized chronic neural probes were seeded with NSCs and incubated in GM or DM for 14 days. NSC-covered probes were implanted in the cortex of adult rats, followed by perfusion and extraction of their brains for immunohistochemistry and other quantification purposes after 24 hrs or 1 week. Brain sections were stained for GFP, astrocytes, neurons, microglia, and macrophages. The stained slices were then imaged using confocal microscopy.

In vitro results: In GM a large number of NSCs were found to be adhered on laminin immobilized surfaces compared to the unmodified control. In addition, the number of NSCs on the surface in the applied force group of the laminin immobilized samples vs. control (without applied force) was significantly higher ($p<0.05$). The DM samples showed that astrocyte differentiation increased with increase of incubation time. While, Nestin positive cells decrease with incubation, suggesting increased differentiation of the stem cells over time. The percentage of neurons and oligodendrocytes was observed to be higher at day 3 and decreased later.

In vivo results: 2-photon microscopy and fluorescent images of the probes show that NSCs incubated in GM adhere well to the laminin modified neural probes. Some of the cells remained attached after insertion and they seemed to stay attached even after extraction. The immunostained tissue sections show less astrocyte activation around the stem cell seeded probes than control after 1 week, suggesting that NSCs may help reduce the astrocytic tissue reaction around the probe implanted in the brain. These results are encouraging and further analysis will be taken to track the fate of these cells after longer period of times.

Possible Interruption of Pilocarpine-Induced Status Epilepticus In Rats Via Concentric Ring Electrode Transcutaneous Electrical Stimulation

Walter G. Besio[1], K. Koka[1], A.J. Cole[2] and F. Zhu [1]
[1]*Department of Biomedical Engineering, Louisiana Tech University-Ruston, LA, USA*
[2]*Epilepsy Service, Massachusetts General Hospital, Harvard Medical School, Boston, MA,* USA.

Rationale:
We sought to evaluate the effect of transcutaneous electrical stimulation (TcES) via concentric ring electrodes on ictal electrographic and behavioral activity and mortality in rats with pilocarpine-induced status epilepticus (SE).

Methods:
Male Sprague-Dawley rats (280-330 g) were briefly anesthetized and three concentric ring electrodes were affixed to their scalps one day before the experiment. Scopolamine methylnitrate (2 mg/kg i.p.) was given 30 minutes prior to pilocarpine. Pilocarpine HCl (310mg/kg i.p) was given to cause long lasting SE. Laplacian EEG was recorded from tri-polar concentric ring electrodes on the scalp. TcES was applied five minutes after the onset of SE. Time-frequency analysis was performed on the Laplacian EEG signals to compare the electrographic activity before and after the application of TcES. Behavior was monitored by inspection. Survival was assayed at 24 h after administration of pilocarpine.

Results:
Control rats (n=13) followed the classic electrographic stages of pilocarpine-induced status epilepticus described by Treimen (1987) and expired on average 16 hours after the pilocarpine injection. Three outcomes were observed in the TcES treated rats (n=31): (A) 13 rats ceased all behavioral and electrical seizure activity within minutes; (B) 11 rats had lessened behavioral activity and lowered ictal frequencies with increased interictal periods; and (C) 7 rats had lessened behavioral activity but no evident changes in the LEEG. The 24 ((A)&(B)) TcES treated rats lived significantly longer than the 13 untreated controls ($p=0.024$, Two-Sample t-Test). Twenty-four hours after the pilocarpine injection, eighteen (58%) of the TcES-treated rats versus three (15.0%) control rats were alive ($p=0.005$, Mann-Whitney U test). All ((A)&(B)) TcES-treated rats recovered to baseline activity, including eating and drinking. By contrast, none of the control rats ate or drank after they entered SE. The time-frequency analysis showed evident differences before and after TcES.

Conclusions:
The application of TcES appears to have increased the survival chances of rats with pilocarpine-induced SE. Positive TcES effects on electrographic and behavioral manifestations of seizure activity were significant and persistent. TcES may represent a novel and effective early treatment for SE. Further testing of TcES via concentric ring electrodes is warranted.

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Investigation of a Biocompatible Flip Chip Under Bump Metallization Scheme for System Integration of Utah Electrode Array

Rajmohan Bhandari [1], Sandeep Negi [1], Loren Rieth [1,2], Michael Toepper [3], Matthias Klein 3, Hermann Opermann [3], Richard A. Normann [4] , Florian Solzbacher [1,2,3]

[1] Department of Electrical Engineering, University of Utah, SLC, UT
[2] Department of Material Science and Engineering, University of Utah, SLC, UT
[3] Fraunhofer Institute for Reliability and Micro integration IZM, Berlin, Germany
[4] Department of Bioengineering, University of Utah, SLC, UT

Material selection is one of the most important tasks for biomedical microsystems. Unlike consumer products or automotive applications, the aspect of biocompatibility has to be taken into account for implantable electronic devices. The assembly process can not be neglected because solder, fluxes and under filler are mostly developed for applications outside the human body. In this work we use flip chip bonding in a novel way which enables the system integration of Utah electrode array (UEA). Conventionally the flip chip process is used to bond a die to a substrate or interposer, we are making electrical interconnects from the Under Bump Metallization (UBM) on the UEA to the solder bumps on the IC. As a result of this the UBM should make Ohmic contact, provide an excellent adhesion (silicide formation) with the underneath Si-substrate. The electrical contact resistance of the UBM /Solder should be minimized. The stress of UBM system should be optimized to avoid film delamination which can cause Si cratering. The interfacial reaction between the UBM layer and the solder bump should be minimum due to its brittle behaviour.

Few metals are well established as biocompatible, and the experiments to date have focused on these materials. This work investigate UBM that consisted of a sputter deposited thin film sequence of Ti/Pt/Au/TiW with respective thicknesses of 50/150/150/100 nm. Ti acts as an adhesion layer, Pt as a diffusion barrier, Au as a wettable metallization and TiW as a wetting stop layer. In order to optimize the deposition conditions for the UBM stack, a 2x2 full factorial Design of Experiments (DOE) was used. The factors investigated using a 2 level design included Ar process pressure (5 and 20 mTorr), and the deposition power (45 and 90 W). The effect of these parameters on the residual stress was studied. An adhesive tape test was performed on UBM, which show showed good adhesion. The residual compressive stress of - 56 MPa in the optimized metallization was measured.

In order to evaluate the integrity of the UBM we did shear test on the optimized metal stack. The Under bump shear test indicates that at 700 cN force on the 100 bond pads, the UBM delaminates completely indicating bad adhesion of the UBM to the substrate. Shear testing of more samples is in progress. Energy Dispersive X-ray analysis EDX was used to investigate the composition from the delaminated bond pad area and 3.46 weight percent of Ti was found. This suggests that the Ti film reacted with the Si to form a silicide. Also, substantial amount of Sn (35.66 weight percentage) was found in the delaminated bond pad area which suggests that an intermetallic compound might have formed which could degrade the mechanical strength of the UBM. Investigation of UBM's composition analysis by Electron Spectroscopy for Chemical Analysis (ESCA) is in progress.

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Validity of the Quasi-static Assumption for Calculating Potentials Generated in Neural Stimulation

Merrill J. Birdno, Chad A. Bossetti, and Warren M. Grill
Department of Biomedical Engineering, Duke University, Durham, NC

Calculation of electric potentials in models of electrical stimulation of the nervous system have typically been carried out using the quasi-static approximation. Under the quasi-static approximation, electric potentials are calculated while neglecting the time-varying reactive components of tissue impedance. To determine the validity of this approach, we compared the solution for the potential generated by a point source electrode in an infinite homogeneous isotropic volume conductor using the quasi-static approximation to the exact inhomogeneous Helmholtz solution. We also simulated strength-duration and threshold-distance curves using a computational model of a myelinated nerve fiber stimulated with the point source electrode. Our results indicate that the extracellular potentials are much more strongly dependent on the selection of an appropriate conductivity than on the inclusion of permittivity parameters in the Helmholtz solution, and that the quasi-static approximation provides an accurate estimation of the scalar potential. For an appropriately selected conductivity and variations in pulse width from 5 to 20 μs, the quasi-static potential estimates had mean absolute errors that ranged from 22% to 56% across the time interval of the pulse as compared to the Helmholtz solution. However, for pulse widths in the range more commonly used for neural stimulation (25 μs - 1 ms), mean absolute errors were between 5% and 18%. For a constant pulse width of 100 μs, the mean absolute errors were constant at 5% across distances from 10 μm to 1 cm from the point source electrode. In the Helmholtz solution, the potential was much more sensitive to changes in the conductivity (doubling or halving the conductivity halved or doubled the potential, respectively) than to changes in the permittivity (doubling or halving the permittivity changed the potential by only 2 - 11%). Simulated strength-duration and threshold distance curves showed deviations of 8% to 20% between the stimulation thresholds of the myelinated nerve fiber when potentials were calculated using either the quasi-static approximation or the Helmholtz solution. These results provide evidence that the quasi-static approximation is an appropriate simplification for estimating scalar potentials resulting from neural stimulation.

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Multilabel Imaging and Quantitative Analysis of Brain Structure in Response to Neuroprosthetic Device Insertion

CS Bjornsson1, G Lin[2], K Smith1, A Tyrell2, YA Al-Kofahi2, D Goodspeed1, B Roysam2, W Shain1

1 New York State Department of Health, Wadsworth Center, Albany, NY

2 Department of Electrical, Computer and Systems Engineering, Rensselaer Polytechnic Institute, Troy, NY

Brain tissue consists of neurons, glia and vasculature woven into an intricate three-dimensional architecture. In order to describe the complex interrelationships among these elements in different brain regions and in response to neuroprosthetic devices inserted into rat cortex, we developed automated image analysis software (FarSight) capable of analyzing confocal images of 100 μm-thick tissue slices labeled with up to 5 immunohistochemical and chemical markers. These rich datasets permit simultaneous investigation of the distribution and morphology of neurons (Nissl), astrocytes (GFAP, GFP), microglia (Iba1) and blood vessels (EBA, laminin). By including a generic nuclear marker we can identify the position of every cell soma and classify them based on intrinsic features including morphology and heterogeneity, and on associations with the other cellular and vascular markers. FarSight first segments structures contained within each channel, visualizes the resulting data in 3D, and computes a rich set of descriptors for each object, as well as customizable associative measurements between two or more object types. These quantitative measurements can be broadly categorized into spatial, intensity-based, graph-based, and associative. Example features include spatial coordinates, volume, surface area, intensity, texture, shape factor, adjacency information, classification of each cell type, volume of cytoplasmic marker, process length and branching, and diameter, length, and branching of blood vessels. To extract high-level associative measurements, graph, geometric distance map and conditional distance were used. Our methodology can be applied to diverse studies that require a quantitative understanding of interactions among multiple components of brain tissue. Distances between different cell types to each other and to the nearest blood vessel were calculated. Microglia were often found in close association with the vasculature. Organizational and morphological differences were observed among different cortical layers and in response to device insertion.

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Brain Computer/Mach Interface

FEEDBACK CONTROL FOR A HIGH LEVEL UPPER EXTREMITY NEUROPROSTHESIS

Dimitra Blana, 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, which 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, 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, six bones and five joints, with a total of nine degrees of freedom. The morphological and muscle contraction parameters were obtained from cadaver studies performed by the Van der Helm group in Delft[1].

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, that 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 currently evaluated in simulation. Its ability to correct for errors is tested by modeling the effects of fatigue and external forces representing obstacles. Subsequently, the controller will be implemented and tested in one individual with high level spinal cord injury.

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Generating Bladder Voiding in a Feline Model by Electrical Pudendal Nerve Block and Sacral Root Stimulation

Adam Boger[1], Narendra Bhadra[1], Tim Bruns[1], Kenneth J. Gustafson[1,2]

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

Bladder sphincter dyssynergia, characterized by the simultaneous uncoordinated contraction of the bladder and external urethral sphincter (EUS), is common after spinal cord injury. EUS contraction can prevent bladder emptying. Current neuroprotheses that activate the bladder via sacral root stimulation require afferent nerve transection to prevent EUS contractions that can prevent voiding. Complete and reversible block of the pudendal nerve, which innervates the EUS, has been demonstrated in animals using High Frequency Alternating Current (HFAC) stimulation. This study sought to demonstrate low pressure, low residual bladder voiding via HFAC block of nerve impulse transmission in the pudendal nerve (PN) and concurrent sacral root stimulation.

Experiments were conducted on two cats under alpha-chloralose anesthesia. Bladder pressures were monitored and bladder volumes were controlled via a dual-lumen suprapubic catheter. Tripolar cuffs were placed bilaterally on sacral spinal roots found to evoke the greatest increase in bladder pressure in response to electrical stimulation. Four additional tripolar electrodes were placed bilaterally on the pudendal nerves, two on each side. Effective bilateral PN block parameters were determined by applying 1 Hz twitch stimulation to the proximal PN cuffs and blocking transmission of impulses to the EUS via HFAC stimulation applied to the distal PN cuffs (1-10Khz 1-25V). Impulse transmission and block were verified by a urethral catheter mounted pressure transducer. Sacral root stimulation was either continuous with duration of 20 seconds or intermittent (2 seconds on and 2 seconds off) with duration of 30 seconds. For trials including PN block, sinusoidal HFAC was applied bilaterally to the distal PN cuffs using the optimal parameters determined previously.

Voiding trials with block emptied a significantly higher percentage of the bladder volume (75% ± 15%, n=30, $p<.001$) than voiding trials without block (5% ± 9%, n=31). Percentages voided during HFAC runs were comparable with percentages voided following bilateral PN transection (74% ± 18%, n=7, $p=.91$). The peak bladder pressure during trials with HFAC block was substantially lower than during trials without HFAC block.

Bilateral HFAC PN block combined with sacral root stimulation produced bladder emptying at low pressures with low residual volumes. Bilateral HFAC PN block may provide the basis for neuroprostheses to control bladder function in individuals with bladder sphincter dyssynergia without irreversible nerve transection.

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Design Of A Magnetorheological Fluid Knee Locking Mechanism For the Hybrid Orthosis System

Thomas C. Bulea[1,2], *Rudi Kobetic, M.S.*[2], *Ronald J. Triolo, Ph.D.*[2,3]

1) *Department of Biomedical Engineering, Case Western Reserve University*
2) *Motion Study Laboratory, Louis Stokes V.A. Medical Center*
3) *Department of Orthopaedics, Case Western Reserve University*

A permanent magnet-electromagnet magnetorheological (MR) fluid knee brake orthosis was designed as a component for the hybrid orthosis system (HOS). The orthosis was designed to provide the ability to lock and unlock the knee joint and supply variable damping force to the knee joint during different phases of gait. This capability is accomplished through the use of a novel permanent magnet-electromagnet MR fluid braking mechanism which is incorporated in the joint of the orthosis. The braking mechanism is comprised of thin metal discs which are alternately coupled to thigh and shank rotation. A permanent magnet located at the axis of the joint prevents relative motion between these discs by introducing a magnetic field in the MR fluid, increasing its yield stress to lock the joint. When energized, an electromagnetic coil wrapped around the permanent magnet core unlocks the joint through cancellation of the permanent magnetic field across the MR fluid, allowing free rotation of the knee joint. Locking and unlocking can occur quickly at any point in the range of motion. Varying the intensity of the supplied electromagnetic field provides intermediate resistance to movement through less than full cancellation of the permanent magnetic field.

The permanent magnet–electromagnet system is energy efficient in that electrical power is only required during joint movement, and fail-safe because the joint will lock to prevent collapse in the event of power failure. Initial design of the MR fluid braking mechanism is presented, including finite element methods used to optimize the magnetic properties of the orthosis and achieve required locking torque. Simulations have shown the MR fluid knee brake is capable of providing greater than 50 N-m of locking torque while offering a resistive torque of only 1 N-m when joint motion is desired.

A prototype of the MR fluid knee brake orthosis is currently being constructed. Future work will include bench and able body testing of the prototype, design refinement, and control strategy development for incorporation into the HOS. Extension of this braking mechanism technology to other joints such as the ankle, hip, or elbow will also be considered.

Topic Area: Materials and Devices

This work was funded by the DoD (Grant #PR043074) and the VA (Grant #B3463R).

Therapeutic Volumes of Tissue Activated During Deep Brain Stimulation

Christopher R. Butson[1], Christopher B. Maks[1], Angela M. Noecker[1], Scott E. Cooper[2], Barbara R. Wolgamuth[2], Benjamin L. Walter[2], Cameron C. McIntyre[1,2]
Cleveland Clinic, 1. Department of Biomedical Engineering, 2. Center for Neurological Restoration, Cleveland, OH, USA

Deep brain stimulation (DBS) is an established therapy for the treatment of movement disorders. However, the inability to predict and visualize the effects of DBS in individual patients has hindered scientific analysis and clinical optimization of this therapy. Here we present a body of work to predict the volume of tissue activated (VTA) during DBS in the region of the subthalamic nucleus (STN), validate the predictions with corticospinal tract and oculomotor nerve thresholds, and correlate the VTAs with clinical outcomes in Parkinson's disease patients.

We developed a Windows-based interactive software system that enables integration of MR/CT imaging data and 3D anatomical models of brain nuclei within the coordinate system of the stereotactic frame. The anatomical models are interactively customized to the patient anatomy and coupled to microelectrode recording data acquired during surgery. 3D visualization of the various electrode tracks and DBS electrode are used to determine anatomical and neurophysiological relationships. These results are then coupled to our detailed computer models of the electric field and neural activation generated by DBS. The stimulation model explicitly accounts for electrode capacitance, electrode impedance, tissue anisotropy, tissue inhomogeneity, and the effects of stimulation parameter adjustments (contact, voltage, pulse width, frequency). Finally, correlations between the VTA and behavioral outcomes are generated for therapeutic and non-therapeutic DBS.

We found that anatomical and electrical localization of the STN is well constrained by the combination of imaging data, anatomical models and microelectrode mapping data. Stimulation thresholds for activation of the corticospinal tract or oculomotor nerve are well predicted by the models of the stimulation spread. Lastly, therapeutic STN DBS is characterized by a VTA that spreads outside the borders of the STN and commonly includes zona incerta and fields of Forel.

Combined analysis of the anatomical, electrophysiological, stimulation and behavioral effects of DBS in a single platform provides a comprehensive picture for scientific analysis. We are currently developing a probabilistic spatial model from 10 STN DBS patients that correlates their VTAs with the surrounding anatomy and therapeutic outcome of the stimulation. Our long-term goal is to use our models of stimulation and interactive software tools to improve the clinical optimization of DBS technology.

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Biomimetic Mechanically-Dynamic Nanocomposites for Cortical Electrodes

Jeffrey R. Capadona[1], Otto van den Berg[2], James P. Harris[1,3], Christoph Weder[1,2], Stuart J. Rowan[2], and Dustin J. Tyler[1,3]

1 Advanced Platform Technology Center, L. Stokes Cleveland VA Medical Center
2 Department of Macromolecular Science and Engineering, CASE, Cleveland, OH
3 Department of Biomedical Engineering, CASE, Cleveland, OH

Materials and Devices

Cortical electrodes offer an intimate interface to the complex activity of the brain. A limiting factor of current technology is the mechanical mismatch with the cortical tissue. While a high modulus electrode is advantageous during insertion, a chronically stiff electrode causes micro-motion, micro-damage, and chronic astrocyic response in the brain tissue. For successful implementation of cortical electrodes the chronic mechanical mismatch must be addressed, while retaining required properties for proper insertion. The objectives to this research are to design stimulus-responsive, mechanically-dynamic polymer nanocomposites, and to use these materials for fabrication of cortical electrodes.

Composites used in this study were modeled after the natural three-phase defense mechanism for the mechanical reinforcement of the skin of *echinoderms.* Our nanocomposites are composed of cellulose whiskers (approximate dimensions 1 μm x 10 nm) as a high-aspect ratio, high-strength reinforcing agent within an elastomeric polymer matrix of an ethylene oxide–epichlorohydrin (EO–EPI) copolymer. Investigation towards the mechanism for mechanical reinforcement was conducted with aqueous suspensions of whiskers. Composites were made by defusing copolymer into a cellulose sol gel with a pre-assembled cellulose network; followed by solvent evaporation and compression molding.

We demonstrated that 50:50 EO/EPI matrix copolymer films containing cellulose whiskers display approximately a 270-fold increase in modulus compared to the neat EO/EPI matrix. Upon activation with stimulus, the reinforcing whisker network is decoupled, resulting in a significant decrease of modulus. This process can be cycled between high modulus and low modulus.

The extension of the general design principles established in this project will result in an entirely new class of bio-inspired artificial nanocomposites for limitless applications in which the mechanical properties can be changed in a controlled and reversible manner.

This work was funded by the Advanced Platform Technology (APT) Center of the US Department of Veterans Affairs.

A Real-Time Model for Use in a Dynamic Arm Simulator

Edward K. Chadwick 1, Ton van den Bogert 2, Dimitra Blana 1, Robert F. Kirsch 1
1 Case Western Reserve University and Cleveland VA FES Center, Cleveland, OH.
2 Department of Biomedical Engineering, Cleveland Clinic Foundation, Cleveland, OH.

A real-time model of the human upper limb has been developed for use in a dynamic arm simulator (DAS). Applications of such a device include training of neural prosthesis (NP) users, development of control algorithms for NP devices and improvement of decoding algorithms for brain-machine interfaces (BMI). The DAS reads movement intent from a user via a BMI, simulates the desired movement and displays the results to the user via a virtual reality environment. The model replicates the dynamics of the arm due to intertia, kinematic coupling and muscle activation dynamics, ensuring the user is presented with a realistic simulation of arm movement and response.

The first iteration of the model is a simple two degree-of-freedom (DOF), horizontal plane model of the arm. The model comprises a shoulder (gleno-humeral) joint and an elbow (humero-ulnar) joint, which allow flexion and extension of the arm in the horizontal plane. There are six muscles crossing the joints: two mono-articular shoulder muscles, two mono-articular elbow muscles and two bi-articular muscles. Joints in the model are represented as geometric structures and the lines of action and moment arms of the muscles are calculated using wrapping objects. Preprocessing of the moment arms allows the model to run much faster than previous models with this level of detail. The model runs approximately 50 times faster than real time on a 3GHz Pentium 4, allowing plenty of scope for increasing the complexity of the model while maintaining real-time speed.

Control of such a system is not trivial due to the presence of non-linear, redundant actuators (muscles), even with a number of muscles and degrees of freedom. Therefore an advanced neural network controller has been developed that allows the user to control the configuration of the arm simulator via the specification of the end point. The neural network provides the non-linear mapping of end-point position error to desired muscle activation. A feedback controller such as a proportional-derivative controller can then be used to control the position of the arm.

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Effects of DBS on Sensorimotor Integration in Rat Model of Parkinson's Disease.

Jing-Yu Chang 1 , Li-Hong Shi 2 , Zhuo-Ming Li 1 , Fei Luo 3, and Donald Woodard 1

1 Neuroscience Research Institute of North Carolina, Winston-Salem NC, 27101.

2 Department of Physiology and Pharmacology, Wake Forest University, Winston-Salem NC 27157,

3 Institute of Psychology, Chinese Academy of Science, Beijing, China,

A variety of sensory abnormalities has been detected in animal models and patients with Parkinson's disease (PD). Such abnormalities disrupt normal motor processing that requires constant sensory feedback to regulate ongoing motor actions. It has been suggested that basal ganglia selectively process or gate specific type of sensory information related to particular behavioral and motor actions.

We have developed a whisker stimulation experiment to test the effect of deep brain stimulation (DBS) on sensory motor integration process in unilateral dopamine lesioned rats. In this test, food deprived rats were trained to respond to the whisker stimulation by catching a food pellet attached to the stimulation probe. Neurological intact rats will respond to whisker stimulation vigorously, catching the food pellet within 0.5 s. In unilateral dopamine lesion rats induced by injection of 6-OHDA into the medial forebrain bundle, responses to whisker touching contralateral to the dopamine lesion were either absence or greatly delayed whereas responses to the ipsilateral whisker touching did not change. DBS of the subthalamic nucleus (STN) in the lesion side significantly improved the responses to the contralateral whisker stimulation. Number of responding trials to whisker stimulation increased and latency of catching food pallet reduced significantly during DBS. These results show clearly that DBS is able to restore motor responses to sensory stimulation. We used an electrophysiological approach to distinguish sensory processes from the motor ones. In a satiated condition, rats ceased to response to the whisker touching after period of stimulation. At this point, the neural response to the whisker touching was largely sensory in nature. DBS of the STN induced a variety of neural responses in the cortical basal ganglia regions. Preliminary results indicated that DBS modified neural responses to sensory stimulation in the cortical basal ganglia regions.

In summary, this study demonstrated that DBS is able to improved sensorimotor integration process in rat model of PD. Modulation of sensory inputs to the cortical basal ganglia system may partially responsible for the effect of DBS.

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Model-Based Analysis of Corticospinal Tract Activation by Subthalamic Nucleus Deep Brain Stimulation

Ashutosh Chaturvedi 1, Christopher R. Butson 2, Scott E. Cooper 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

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is an established therapy for medically intractable Parkinson's Disease. However, quantitative understanding of the interaction between the electric field generated by DBS and the underlying neural tissue is lacking. This study concentrated on STN DBS of the corticospinal tract (CST). The CST is a major fiber pathway within the internal capsule, defining the lateral border of the STN. Consequently, STN DBS can generate motor evoked responses from activation of the CST. Clinically, CST activation is an unwanted side-effect of the stimulation. However, the generation of muscle contractions via stimulation of the CST represents a direct link between STN DBS, known neural substrates, and clinically measurable behaviors. Therefore, we developed a patient-specific model of STN DBS to study stimulation spread to the CST and compared our theoretical predictions to clinical measurements from that patient.

Our patient-specific model combined both anatomical and diffusion tensor magnetic resonance imaging (MRI) data. The anatomical MRI was used to define the position of the DBS electrode in the patient's brain. Diffusion tensor MRI was used to define axonal trajectories of the CST. In addition, the diffusion tensor MRI was used to define 3D tissue anisotropy and inhomogeneity surrounding the DBS electrode. The electric field generated by STN DBS was calculated with a finite element model (FEM) and applied to multi-compartment cable models of myelinated axons. One hundred axon models were positioned within the anatomical context of the FEM such that they followed the path of the CST. Stimulation thresholds were calculated for action potential generation in the CST axon models and compared to clinical CST thresholds defined from electromyographic (EMG) recordings from eight muscle groups in the arm and leg of the STN DBS patient.

CST activation was calculated with FEMs that ranged from an electrostatic, homogeneous, isotropic model to a model that incorporated the capacitance of the electrode-tissue interface, electrode encapsulation, and diffusion-tensor based 3D tissue anisotropy and inhomogeneity. Coupled evaluation of the model and clinical data showed that accurate prediction of CST thresholds required our most detailed patient-specific model. In addition, the simplifications and assumptions typically utilized in neurostimulation models substantially overestimate neural activation.

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Low-Frequency Electrical Field Modulation of Neural Activity in a Chronic Seizure Model

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

1 Engineering Sciences and Mechanics, Pennsylvania State Univ., University Park, PA.
2 Electrical and Computer Engineering, George Mason Univ., Fairfax, VA.
3 Children's National Medical Center, Washington, D.C.
4 Neurosurgery, Pennsylvania State Univ., University Park, PA.

Topic Area: Models and Stimulation Paradigms.

Low-frequency (<<100Hz content) electrical fields have been demonstrated to modulate neural activity both in slice preparation as well as in acute animal experiments (Richardson et al., Epilepsia 44(6):768-77, 2003). Such modulation is advantageous over pulse stimulation for use in neural prosthetics both because it has an excitatory and inhibitory, graded effect and because with proper instrumentation can be done with minimal recording artifact. Therefore, this mode of interaction is ideal for use with continuous feedback controllers. We present here the first demonstration of electric field modulation in chronically implanted animals.

All work was carried out under IACUC approval. Sprague-Dawley rats (300 g) were anesthetized and implanted with iridium-oxide coated stimulation and recording electrodes located in various parts of the hippocampus, along with stainless steel cranial screw electrodes (n = 5 rats). Tetanus Toxin (5 ng in 1ul) was injected into the right ventral hippocampus to induce spontaneous seizures, which are observed with a peak rate of ~30/day in weeks 2-4 after implantation. Custom recording hardware was used to provide high fidelity recordings of neural activity with minimal stimulation artifact.

Residual stimulus artifact was identified and subtracted by estimating the transfer function between applied current and recorded field potential using cross-spectral analysis. This permits stimulation artifact cancellation in the presence of arbitrary, broad band (0.01-50 Hz) stimulation patterns.

Direct modulation with electric fields was observed in response to periodic low frequency (9-15 Hz) sinusoidal stimulation. Clear entrainment of activity was transiently observed in recordings of hippocampal activity contralateral to the stimulation both at seizure onset and termination. In addition, observations of interaction include seizure occurrence reduction under various stimulation protocols.

These results are a step in the development of an implantable, closed-circuit stimulation controller with the ultimate goal of electronic seizure suppression.

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Cortical Microelectrode Investigations of Binaural Acoustic-Electrical Interaction in the Auditory Cortex of Rats Implanted with a Cochlear Implant

Lavanya Krishnan and Ryan S Clement

Department of Bioengineering, The Pennsylvania State University, University Park, PA

Patients with residual hearing in one ear have increasingly become candidates for unilateral cochlear implants. This raises several interesting questions: Will the acoustic hearing in the non implanted ear interfere with the auditory percept created due to the electrical stimulation, or on the contrary can the acoustic hearing be used to fill the gaps in electrical hearing? It has been suggested (Kong et al. 2004) that acoustic cues could provide useful low frequency information and fine-time structure information, necessary for speech recognition in noise as well as for melody recognition. Our research aims at exploring the electrophysiological basis for such interactions in the auditory cortex with the use of intracortical microelectrode arrays. Rats were implanted in the auditory cortex with a 2x8 tungsten micro wire array. The contralateral ear was deafened using neomycin and the cochlea implanted with a custom multi-channel cochlear electrode. Bi-phasic electrical stimulation pulse bursts were provided through the cochlear electrode simultaneously with free field acoustic stimulation (tone pips; noise bursts). To date we have been successful in implementing the model, demonstrating successful recording of single and multi-unit recording activity modulated by both acoustic and electrical stimulation. Preliminary results show slight modulation of the neural response with the addition of the acoustic stimuli. Ongoing studies investigate the effect of spectral content and evaluate temporal properties such as degree of time locking. The model provides for interesting studies of binaural interaction and the integration of significantly different stimulation modes. Knowledge gained from these experiments may lead to more optimal stimulation strategies for cochlear implant users to take advantage of residual hearing.

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Topic Area: Auditory Prosthesis

Voltage Transients and the Compliance Limited Strategy for Reversible Charge-injection

Stuart F. Cogan,[1] Philip R. Troyk[2]
1. EIC Laboratories, Inc. Norwood MA
2. Illinois Institute of Technology, Chicago IL

Historically, reversible charge-injection limits for neural stimulation have been derived from *in vitro* measurements of voltage transients at electrodes subjected to current pulses in an inorganic buffered saline electrolyte that approximates the buffer and NaCl concentration of the extracellular fluid. The maximum safe charge has been defined as that which polarizes the electrode to the equilibrium potential limit for the reduction or oxidation of water. The limits of electrode polarization during a current pulse are determined by subtracting the initial voltage excursion, often called the access voltage or iR-drop, from the maximum driving voltage measured against a non-polarizing reference electrode. A tacit assumption is often made that by employing constant-current pulses, the injected charge can be precisely controlled to avoid water electrolysis or other irreversible processes at the electrode. With this assumption, the magnitude of the voltage required to drive a current pulse is not a factor in determining safe charge-injection since the access voltage is dropped in the tissue rather than across the electrode-electrolyte interface. In the present work, we examine this assumption and identify some limitations of the approach in avoiding irreversibility at electrodes subjected to constant-current pulsing. The driving voltage for a current pulse includes an ohmic drop due to ionic resistance in the tissue and an equilibrium potential change at the electrode. However, concentration and activation polarization also occur and impact charge-injection reactions. The origin and relevance of each element in the voltage transient during a constant-current pulse is discussed. How differences in the *in vivo* and *in vitro* environments, primarily tissue encapsulation and diffusional tortuosity, may affect electrode polarization are also described. A strategy of injecting charge using constant current pulses with a driving or compliance voltage limit that prevents polarization of the electrode beyond a fixed potential limit is presented and discussed in the context of the electrochemical and transport processes that control charge injection. Comparisons of *in vivo* and *in vitro* voltage transients for chronically and acutely implanted electrodes are provided for illustration.

Sputtered Iridium Oxide Charge-Injection Coatings for Stimulation and Recording Electrodes

Stuart F. Cogan,[1] Timothy D. Plante,[1] Julia Ehrlich,[1] Douglas Shire,[2] Marcus Gingerich[2]
1. EIC Laboratories, Inc. Norwood MA
2. Center for Innovative Visual Research, Boston VA Hospital, Boston MA

Thin sputtered iridium oxide films (SIROFs) have been investigated as charge-injection coatings for neural recording and stimulation electrodes. The SIROF was deposited by reactive DC magnetron sputtering onto gold electrode sites patterned on flexible polyimide substrates. The effect of SIROF thickness from 250 nm to 1000 nm and electrode area from 2,000 μm^2 to 125,600 μm^2 on the electrochemical and charge-injection properties were investigated. The electrochemical characterization included cyclic voltammetry (CV), impedance spectroscopy (EIS), and charge-injection capacity as a function of potential bias from 0.1-0.7 V (vs. Ag|AgCl). The maximum charge-injection capacity was defined by the electrochemical potentials for oxidation and reduction of water which are approximately 0.8 V and –0.6 V vs. Ag|AgCl, respectively.

SIROF reduced electrode impedance in a manner similar to that observed with activated iridium oxide (AIROF) coatings. However, unlike AIROF, the SIROF impedance remained consistently low over a broad potential range from –0.6 V and 0.7 V vs. Ag|AgCl. This insensitivity to potential is not typical of either activated (AIROF) or electrodeposited iridium oxide (EIROF), which both become high impedance at potentials more negative than 0.0 V (Ag|AgCl). SIROF charge-injection capacity was a strong function of electrode area varying from 2 mC/cm^2 to 4.5 mC/cm^2 as the area decreased from 125,600 μm^2 to 2000 μm^2 (0.4 ms cathodal pulses, 0.5 V Ag|AgCl bias). The *in vitro* stability of SIROF was evaluated by long-term pulsing at 1 mC/cm^2 (1 ms pulse width, no bias) for 250 days in an inorganic electrolyte model of interstitial fluid (model-ISF). SIROF electrodes generally survived this challenge without degradation, although loss of adhesion between the gold metallization and polyimide was observed on some electrodes. SIROF electrodes were more stable electrochemically and mechanically (abrasion resistance) than AIROF electrodes as judged by over-potential and tape adhesion measurements.

The SIROF exhibits charge-injection properties similar to those of AIROF or electrodeposited iridium oxide (EIROF) and may have the advantage of better mechanical and electrochemical stability relative to other iridium oxides. The application of SIROF to planar and conical microelectrodes is also discussed. These preliminary results suggest that SIROF could be a useful charge-injection coating for neural prostheses, particularly on multielectrode arrays that are fabricated by thin-film processing methods.

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Implementation of A Neuroprosthesis in High-Level Spinal Cord Injury

Andy Cornwell, Dimitra Blana, Juan Gabriel Hincapie, William Memberg, Robert Kirsch

Dept. of Biomedical Engineering, Case Western Reserve University

A neuroprosthetic system has been implemented in one subject with high tetraplegia. Individuals with that level of injury have almost complete loss of motor function, and very few rehabilitation options, resulting in their total dependence on others for all aspects of care. This system applies functional electrical stimulation to the paralyzed upper extremity muscles, in order to restore lost arm and hand function.

The system uses two implanted IST-12 stimulators, which provide for stimulation of a total of 24 muscles and myoelectric (EMG) recording from four muscles. It uses 6 cuff electrodes, with a total of 9 stimulation channels, and 15 intramuscular electrodes.

In order to determine the optimal muscle set to be stimulated by the neuroprosthesis, a computer model of the arm was used. This was necessary because there are a large number of muscles that must be controlled in high tetraplegia, so purely experimental methods are impractical. The model was customized to simulate a person with high level spinal cord injury, and different sets of paralyzed muscles that can be stimulated were included. The stimulation channels were chosen according to the results of the model simulations.

The system includes four EMG recording electrodes to be used as a command source for the position of the arm in space. The user of the neuroprosthesis is currently training to isolate the four signals with a software task involving several targets and a cursor. She also uses these signals to control simple arm movements in one-dimensional space.

Ultimately, the user will generate commands for more complicated arm movements, and a feedback controller will drive the activation of the appropriate muscles so that the arm follows the desired commands. It will be based on model predictions, and position feedback from body-mounted sensors. The feedback is necessary because voluntary correction for errors is not possible due to the high level of injury. At this time, the feedback controller is being tested in simulation, and the model predictions are being evaluated with the implementation of pre-programmed stimulation patterns.

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A Wearable Monitor for Movement Disorders in Parkinson's Disease

Carlo J. De Luca [1,2.4], Serge H. Roy [2], S. Hamid Nawab [3]

1 Delsys Inc., Boston, MA
2 NeuroMuscular Research Center, Boston University, Boston, MA
3 Department of Electrical and Computer Engineering, Boston University, Boston, MA
4 Department of Neurology, Boston University School of Medicine, Boston

The complex and unpredictable nature of movement disorders in patients with Parkinson's disease (PD) presents a formidable challenge to developing effective measurement tools for assessing their motor function. Current self-report methods, such as patient diaries, are less than optimal for tracking the variety of primary and secondary movement disorders of the disease, which fluctuate and are compounded by complications of long term pharmacological treatment. The difficulty in accurately monitoring these movement disorders may impose a significant obstacle to properly managing interventions such as DBS, which must be carefully adjusted to the individualized needs and baseline status of the patient.

Recent advancements in wearable sensor and signal processing technologies have raised the prospects for an unobtrusive Personal Status Monitor to automatically track movement disorders and mobility status in patients undergoing DBS or pharmacological treatment interventions. We have been developing the underlying technologies needed to implement such a system based on electromyographic (EMG) and accelerometry (ACC) body-worn sensors. Progress to date has included the development of a portable wireless data acquisition system which can be adapted for use with hybrid sensors that combine EMG and ACC detection. The system has been developed to deliver high-fidelity wireless data transmission, from the patient's home to the health care provider, in a manner similar to present-day Holter monitors or other Telemedicine approaches to health care.

Parallel efforts by us have been directed at developing algorithms, and their software implementation, for pattern recognition and interpretation of the EMG and ACC signals. Data collection experiments have been designed and initiated to advance the algorithm development in a hierarchical manner starting from highly standardized activities to free-form activities which approximate real-world conditions. A Blackboard-based software framework of our own design (Nawab & Lesser, 1992) is being adapted to integrate Artificial Neural Networks (ANN), Rule-Based Systems (RBS), and Iterative Correlation Analysis (ICA) for feature extraction, mapping of states to temporal epochs, and resolving identification problems due to the simultaneous presence of motor abnormalities and/or extraneous motor activities. Initial algorithm development will be supplemented by the inclusion of data acquired from PD patients undergoing DBS treatment, where the adjustment of stimulation parameters can provide a direct means of monitoring changes in movement disorders.

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Effective Deep Brain Stimulation Eliminates Disordered Neural Activity

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] Department of Neurosciences, Cleveland Clinic Foundation, Cleveland OH
[3] Third Department of Medicine, Shinshu University School of Medicine, Matsumoto, Japan

High-frequency stimulation of the subthalamic nucleus or internal segment of the globus pallidus alleviates the symptoms of Parkinson's disease. Despite widespread use and clinical success, the mechanisms by which deep brain stimulation (DBS) reduce motor symptoms are not fully understood. Previous studies have focused on DBS-induced up- or down-regulation of neuronal firing rates in the relevant basal ganglia and thalamic regions. We hypothesize that neuronal firing rates are less important than the patterns of activity the neurons exhibit, and that clinically effective DBS blocks the highly disordered activity patterns that arise in the basal ganglia and thalamo-cortical circuits in persons with Parkinson's disease.

We used the MPTP-primate model of parkinsonism to quantify the neuronal effects of high-frequency stimulation (HFS) and low-frequency stimulation (LFS) of the subthalamic nucleus. During stimulation, we recorded spike times in single neurons of the globus pallidus internal (GPi) and external (GPe) segments and the ventral anterior (VA) and ventral posterior lateral oralis (VPLo) thalamus. To reduce all firing pattern changes to a single metric, we calculated the firing pattern entropy from the spike times. Disordered spike patterns have a high entropy while fairly regular spike patterns (e.g., a constant firing rate) have a low entropy.

Entropy increased in response to LFS ($p < .02$ independently in each region) by 0.26 ± 0.09 bits/spike across regions. This increased firing pattern disorder is consistent with previous work that shows LFS exacerbates movement disorder symptoms. Entropy decreased in response to HFS ($p \leq .002$ independently in each region) by 0.63 ± 0.27 bits/spike across regions. Thus entropy changes in all regions parallel symptom exacerbation and suppression. In contrast, neuronal firing rates were not significantly changed by DBS except in the external globus pallidus, which exhibited a 30 ± 6 Hz firing rate increase in response to HFS ($p < .001$). These data suggest that the clinical effectiveness of DBS is mediated through the ability of HFS to suppress disordered firing patterns in the basal ganglia and thalamo-cortical circuits.

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Wide-field Retinal Prosthesis with Large Area Polyimide Microelectrode Arrays

Helmut Eckhardt 1, Stefan Ufer 1,
Hossein Ameri 2, Tanapat Ratanapakorn 2, Ricardo Freda 2, Mark Humayun 2, and James Weiland 2
1 Premitec, Inc. Raleigh, NC
2 Doheny Eye Institute, University of Southern California, Los Angeles, CA

Retinal implants are intended to give sight to people with outer retinal disease such as retinitis pigmentosa and age related macular degeneration. All retina implant systems tested to date have a limited field of view. Both the subretinal and epiretinal devices in clinical trials subtend less than 10 degrees of visual angle.

Electrode arrays must be larger than 5 mm in diameter to cover 20 degrees or more. However, a surgical limit of 5 mm on the size of a pars plana incision will limit the size of an electrode that can be inserted, if the electrode is rigid. Our results from Phase II demonstrate insertion and chronic implantation of a 10 mm wide, in-active electrode array made possible by using a foldable device that unfolds after insertion.

The purpose of this project was to develop a microfabrication process for large area, highly flexible microelectrode arrays and to assess the feasibility of surgical implantation of large epiretinal array through a small sclerotomy and to evaluate the mechanical effect of the arrays on the retina.

Four large epiretinal arrays, each 10 mm in diameter, were chronically implanted in four dogs. The arrays are made of a flexible polymer (polyimide) and are designed to allow overlapping of different parts. They are fabricated using a special microfabrication process and a proprietary biocompatible encapsulation that protects the arrays and ensures long term functionality in the eye. Surgical implantation involved standard pars plana vitrectomy. The array was introduced into the vitreous cavity after one of the slcerotomies was extended to about 5 mm. The arrays regained its original shape spontaneously and were fixed to the retina with a Grieshaber retinal tack.

All arrays appeared to conform to the curvature of the retinal surface at the end of surgery, except in one case. Follow up examinations with OCT showed partial separation of the arrays from the retinal surface in all cases. In all cases there was minimal to moderate vitreous hemorrhage from sclerotomy wounds at the end of surgery (after removal of the infusion terminal), which was spontaneously resolved within two to three weeks without recurrence. Other findings include retinal pigmentation and corresponding leakage on fluorescein angiogram around the tack and some other areas in almost all cases, retinal fold at the edge of the array in three cases, and retinal tear at the edge of the array in one case.

This study demonstrated the feasibility of implantation of large epiretinal arrays through a small sclerotomy. Long-term biocompatibility issues that need to be addressed relate to

pressure on the retina at the edges and maintenance of close proximity between the array and retina.

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Reducing the excitability of spinal motoneurons by extracellular stimulation of electrical fields and current pulses: A modeling study

Sherif M. ElBasiouny 1,2 and Vivian K. Mushahwar 1,2

1 Department of Biomedical Engineering, University of Alberta, Edmonton, AB
2 Centre for Neuroscience, University of Alberta, Edmonton, AB

The objective of the present study was to investigate the effect of different modes of electrical stimulation, i.e., extracellularly-applied electrical fields and extracellularly-injected current pulses, for reducing the increased excitability of spinal motoneurons seen following injuries to the central nervous system. A compartmental cable model of a cat α-motoneuron was developed that included the realistic motoneuron dendritic morphology, realistic dendritic distribution of Ia-afferent synapses, and dendritic $Ca_v1.3$ channels distributed over the dendrites in a manner that matched a wide set of experimental measurements (ElBasiouny et al., 2005).

Our results suggest that weak AC and DC electrical fields could suppress the excitability of motoneurons and reduce their firing rate by modulating the magnitude of their dendritic persistent inward current (PIC). This effect was obtained with different field directions (rostrocaudal, dorsoventral, and mediolateral axes of the spinal cord), intensities, and polarities. The reduction in motoneuronal excitability resulted from the interaction between the field-induced polarization, the relative positional symmetry of the soma with respect to the dendritic tree of spinal motoneurons, and the distribution and activation level of the dendritic voltage-gated channels. The net effect of the field-induced differential polarization was a reduction in the magnitude of the dendritic PIC reaching the soma due to the nonlinear characteristics of the Ca^{+2} PIC-mediating channels. The end result was a linear relationship between the intensity of the applied field and the induced reduction, or even blockage, of firing rate. The frequency-current (F-I) relationship became linear in shape with shallower slope indicating reduced motoneuronal excitability.

For extracellularly-injected current pulses, our results suggest that low-amplitude, high-frequency, charge-imbalanced biphasic pulses could reduce the excitability of spinal motoneurons. These pulses interfere with the dynamics of Na^+ channels at the soma and initial segment, structures with the lowest firing threshold, and hyperpolarize them causing a reduction, or even blockage of motoneuronal firing. Because of their low net DC current and charge density per phase, these pulses could be tolerated safely by the tissue as charge-imbalanced biphasic pulses have greater safety limits than those for charge-balanced and monophasic charge pulses (Scheiner et al., 1990). Electrical stimulation provided by these pulses reduced the slope of the F-I relationship and made it linear in shape.

The aforementioned electrical stimulation paradigms (electrical fields and pulses) could provide a potential rehabilitation intervention for suppressing the hyperexcitability of spinal motoneurons after spinal cord injury; hence, reducing the severity of motor disorders (e.g. spasticity) after the injury.

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Stability of Human Walking at Different Velocities

[1,2]Vanessa Q. Everding, [1,2]Anirban Dutta, and [2]Elizabeth C. Hardin
[1]Case Western Reserve University,
[2]Cleveland FES Center, Louis Stokes Cleveland VA Medical Center, Cleveland OH, USA

Studying walking stability is an important part of determining falling mechanisms and can aid in prevention of falls, thereby reducing fall-related injuries. Traditionally, walking stability has been measured heuristically; that is, by measures based on logical assumptions about what causes falls. Alternatively, non-traditional methods provide a mathematical analysis of human locomotion as a dynamical system. Although several traditional and non-traditional measures have been studied and published, a strong correlation between these measures and a subject's propensity to fall has yet to be presented. The purpose of this study is to compare some traditional and non-traditional measures of walking stability. The long-term aim of our work is to validate a method for stability analysis of pathological gait which can aid in the understanding and prevention of falling.

Two healthy subjects who had no known neuromuscular disorders were recruited for this study. The subjects walked on a motorized treadmill (ADAL3D-F-COP-Mz, HEF Medical Development, France) at three different walking speeds: their preferred speed, 50% slower than preferred, and 50% faster than preferred. Lower extremity limb trajectories and joint angles were collected over 4 minutes of walking at each treadmill speed via a seven-camera Vicon motion capture system (Oxford Medics, UK). Step length and swing-stance ratio were calculated and differences between the right and left step length were compared for each step of each trial at each speed. Divergence between state-space trajectories was calculated over time, and the natural log of its mean was plotted over time. The largest finite-time estimate of the Lyapunov exponent was estimated from the slope of the linear fit of this curve.

Analysis showed that both traditional and non-traditional measures of lower extremity stability were sensitive to walking speed. At the slower walking speed, we noted increased variability in step length and decreased largest Lyapunov exponents, or increased local stability. Disparity between these measures may be explained by inherent differences in measures of variability vs. measures of system stability. Percent differences are measured with respect to average values; while Lyapunov analysis examines behavior of the trajectories as a system that describes the studied motion. Lyapunov analysis may therefore provide a more accurate measure of the stability of the *entire* lower extremity system.

This exploratory study has been expanded to investigate healthy subjects during normal and constrained walking. More subjects have been recruited and additional non-traditional methods of analysis are being used examine the data. The purpose of the expanded study is to provide a definitive analysis of some recently published stability measures, in order to direct future research toward consensus on a validated measure.

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3-D In Vitro Model Systems for Studying Tissue Impedance

J Frampton[1], M Hynd[2], A Gupta[3], CS Bjornsson[2], G Lin[3], B Roysam[3], JN Turner[1,2], W Shain[1,2]
[1]Department of Biomedical Sciences, University at Albany, [2]Center for Neural Communication Technology, Wadsworth Center, Albany NY and Rensselaer Polytechnic Institute, Troy NY.

Following insertion of neuroprosthetic devices into the cortex a series of events occur that result in reactive cell and tissue responses. Some of these changes are initiated by device insertion, while others respond to the presence of the device itself. While it is possible to study these events following tissue fixation using immunohistochemistry, the only real-time assessment is device performance, e.g numbers of units recorded or signal amplitude. Evaluation of tissue impedance may provide another method for real-time assessment. Correlations of changes in impedance spectra with extent of tissue damage have been made (Williams et al, in preparation). We are taking several approaches to studying how changes in tissue impedance correlate to tissue damage. One of these is to use *in vitro* 3-D tissue constructs to determine how cell density and type, and changes in cell morphology contribute to tissue impedance spectra. These data can then be used to test computer generated models for predicting changes in cell and tissue organization around inserted devices.

3-D tissue constructs were made using functionalized alginate hydrogels as scaffolds for cell culture. Alginate was functionalized by covalently attachment of GRGDY peptides using aqueous carbidiimide chemistry. The efficiency of functionalization was determined using MALDI-TOF mass spectroscopy. 3-D constructs were made by suspending different numbers of cells in alginate solutions. Alginate was polymerized by exposing gel solutions to 200 mM $CaCl_2$ through MilliPore tissue culture inserts. Hydrogels were polymerized on planar microelectrode arrays and the thickness of the 3-D construct was controlled by total volume of the cell-alginate mixture. 3-D construct impedance was measured and 3D image sets were collected to map the position of cells inside the gels. Impedance was measured as a function of cell density, type, and morphology. Computer reconstructions of cell distribution in the in vitro 3-D constructs were created and compared to similar reconstructions of brain tissue where astrocytes, microglia, neurons, and vascular elements are mapped. These mapped data were then used to construct computational models of tissue impedance. Density and morphology changes in the 3-D were used to test the robustness of the tissue impedance models.

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Decoding of Local Field Potentials in Different Layers of Rat Motor Cortex

Gregory J. Gage[1], Chie Kawahara[1], Shani E. Ross[1]
Timothy C. Marzullo[2], and Daryl. R. Kipke[1,3]

[1] Department of Biomedical Engineering, University of Michigan, Ann Arbor, MI
[2] Neuroscience Program, University of Michigan, Ann Arbor, MI
[2] Department of Electrical Engineering, University of Michigan, Ann Arbor, MI

Topic Area: Brain-Computer Interface

Local field potentials (LFPs) have been proposed for use in controlling neural prosthetic devices because they can provide reliable motor and sensory-related information, and can easily be recorded over long periods of time. While studies have shown that directional information about motor movements can be inferred from LFPs, it is not known at what depth these signals should be recorded from in order to maximize the amount of movement information.

Towards this end, we used a directional motor task in Long Evans rats, while sampling LFPs with an electrode consisting of 16 vertical recording sites that were evenly-spaced 100um apart. This allowed for simultaneous recording of all layers of the motor cortex. Both time domain voltage traces, and time series of the power at specific frequency ranges of LFPs during movements were then analyzed using k-means clustering to determine directional information as a function of depth. Here we report our initial findings that superficial layers (II/III) of motor cortex may provide more information about movement directions then deeper layers.

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Mechanics of Neuronal Probe Insertion at Micrometer Scales

A. M. Ortega[1], K. Gall[2], D. Restrepo[3], A. A. Sharp[3]

[1]Dept of Mech Eng, Univ of Colorado, Boulder, CO, [2]Sch of Materials Sci and Eng, Georgia Institute of Technology, Atlanta, GA, [3]Dept of Cell and Dev Biol, UCDHSC, Aurora, CO.

Recently, there has been significant advancement in the methodology for chronic recording and stimulation of the central nervous system. However, in order to develop, design and optimize the next generation of neuronal probes, it is necessary to understand the mechanics of probe insertion at relevant length scales. Little work has been done at micrometer scales to understand the mechanical interaction of neuronal probes with brain tissue during implantation. The purpose of this study was to investigate micrometer scale penetration mechanics of brain tissue *in-vivo*. Cylindrical stainless steel probes were inserted (1.5 mm) into the brain of anesthetized mice. The resulting forces were measured throughout the insertion and removal of the probe. The following parameters were changed: probe size (100 μm vs. 200 μm diameter), probe geometry (flat vs. sharpened tip), insertion rate (822, 104, or 11 μm/s), insertion location (olfactory bulb vs. cortex) and the presence or absence of dura. A decrease in probe diameter resulted in an overall decrease in penetration forces. Flat probe tips produced a two-part loading path upon insertion. First, the probe only compressed the tissue resulting in a near linear increase in force as a function of depth. Then, the probe penetrated the tissue and began to tear through it resulting in either a plateau or decrease in the loading-displacement slope. The sharpened probe tips produced a more constant loading-displacement slope during insertion and lower forces overall. Due to the viscoelastic properties of the brain tissue, slower insertion rates caused a decrease in tissue modulus and lowered the initial loading slope for the insertion of the flat probe. Interestingly, probe insertion into the cortex required higher penetration forces compared to that of the olfactory bulb. Lastly, removal of the dura resulted in a dramatic decrease in penetration forces. Mechanical properties of the brain tissue were extracted from the force displacement curves and knowledge of the probe shape and stress/strain fields. This study provides a basic understanding of how simple design and insertion method modifications influence the insertion mechanics and mechanical properties of brain tissue and will aid in design optimization for future chronic electrodes.

Theme: Electrodes

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Stimulation and Blockade of the Pudendal Nerve Using Transcutaneous, Capacitively Coupled Electrical Stimulation

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

Lower urinary tract dysfunction often occurs as a result of spinal cord injury and a variety of neurogenic and non-neurogenic conditions. After spinal cord injury, concomitant contraction of the bladder and sphincter, or bladder-sphincter dyssynergia, can prevent voiding leading to elevated intravesical pressures and upper urinary tract deterioration. Attempts have been made to develop neural prostheses to restore bladder and sphincter function after spinal cord injury, however many of these devices have been ineffectual or poorly tolerated by patients.

We are investigating a stimulation technique that uses implanted electrodes capacitively coupled to surface stimulation electrodes. This "stimulus router system" (SRS) consists of a subcutaneous pickup electrode made from a metal disk or deinsulated wire that is connected to a stimulating electrode such as a nerve cuff via an insulated wire. The cathode of a pair of adhesive surface electrodes was positioned directly above the subcutaneous pickup electrode. The pickup electrode typically captures 10%-15% of the current passing between the surface electrodes and routes it to the connected stimulating electrode. Nerve cuffs or hook electrodes were placed on the pudendal nerves of isoflurane anesthetized cats. The nerve cuffs were connected to a SRS. Low-frequency stimulation (10-30 Hz) produced contractions of the external urethral sphincter and generated intraurethral pressures greater than 60 mmHg. Interleaved stimulation at 10 Hz allowed stable contractions to be maintained for over 1 minute with little sign of muscle fatigue. High-frequency stimulation of the distal pudendal nerve (200 Hz - 2 kHz) produced varying degrees of nerve blockade resulting in reductions in intraurethral pressure induced by proximal stimulation of the pudendal nerve with low-frequency pulse trains. Reductions in intraurethral pressure to baseline levels were achieved. Upon cessation of high-frequency stimulation, the intraurethral pressure immediately increased indicating that the response was not due to muscle fatigue.

These data indicate that the SRS can be used with both low and high-frequency stimulation waveforms to produce maintained contractions or a reversible blockade of sphincter contraction. The implanted portion of the SRS is completely passive and alleviates the need for complicated and expensive implantable stimulators. Such a device could further efforts to develop a neuroprosthesis for lower urinary tract control after spinal cord injury.

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Intensity Discrimination in Single and Multi-electrode patterns in Cochlear Implants

Ashmita Gaur[1 2], Robert V. Shannon[1,2]
1 Department of Auditory Implants and Perception, House Ear Institute, Los Angeles, CA
2 Department of Biomedical Engineering, Los Angeles, CA

In multi-channel cochlear implants, an electrode array is inserted in the cochlea so that different auditory nerve fibers can be stimulated at different places in the cochlea. Extensive psychophysical studies have mostly shown a poor correlation with speech recognition performance. One possible reason for this lack of correlation is that the psychophysical tests are typically performed on single electrodes whereas speech presents a dynamically changing stimulus across the entire electrode array. It is possible that psychophysical performance is quite different for single electrodes compared with multi-electrode activation, due to peripheral interactions between electrodes or to central interactions or both. The present experiments measured intensity discrimination on single electrodes and in multi-electrode stimulation as a function of level. Stimuli were presented at 250 pulses/sec/electrode or 1000 pulses/sec/electrode on single electrodes and on 5, 10 and 15 electrode clusters, stimulated with interleaved biphasic pulses. Intensity discrimination on a single target electrode was measured as a function of level and as a function of the amplitude of the other electrodes in the multi-electrode complex. Differences in intensity discrimination for single and multi-electrode complexes presumably reflect a combination of peripheral interactions between electrodes and central integration of information across electrodes (profile analysis). The relevance multi-electrode measures of psychophysical capabilities for speech pattern recognition will be discussed.

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A Switched-Capacitor Based Neurostimulating System for Low-Power Head-Mounted Deep Brain Stimulators

Maysam Ghovanloo[1] and Richard Murrow[2]

[1]*Department of Electrical and Computer Engineering, North Carolina State University, Raleigh, NC*
[2]*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 neurological movement disorders. The therapy involves implantation of small electrodes in deep brain structures, connected to a pulse generator, which is currently so bulky that it must 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. In addition, even though implantation of the DBS electrodes in the brain takes place under local anesthesia, the stimulator and subcutaneous interconnect implantation require general anesthesia, imposing further risks and financial burden on the patient and healthcare system.

We are currently developing a significantly smaller, more efficient, integrated microstimulator with system on a chip (SoC) architecture that can be practically attached to the head at the point of electrode entry to the brain. Existing DBS circuits, inherited from the pre-existing cardiac pacing technology, only generate square-shaped pulses and control the stimulus pulse width, frequency, and either voltage or current amplitudes. *Voltage-controlled stimulation* (VCS) provides great 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. We have designed a 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. The SCS stimulus pulses are inherently charge balanced and can be applied in a variety of schemes such as mono/bi -polar and mono/bi-phasic. This innovative technique is expected to substantially simplify the pulse generator architecture and reduce its size and power requirements.

So far we have developed a discrete prototype stimulator capable of generating VCS, CCS, and SCS stimulus pulses in 0~10 V, 0~10 mA, and 0~10 μC range, respectively, with accurate input-output power measurement capability. We will use this prototype stimulator in acute *in vitro* brain slice and cell culture preparations as well as *in vivo* experiments. These setups will be equipped with neurophysiological activity measurement tools such as intrinsic optical signal (IOS) to evaluate and compare the efficacy and efficiency of the three stimulation techniques (VCS, CCS, and SCS) for various neuroprosthetic applications including DBS.

Finite element analysis (FEA) will be used to simulate the stimulus current distribution in 3-D tissue volume conductors filled with excitable neuron models. The purpose of these computer simulations is to observe the volume of the neural tissue being activated using each stimulation technique. A combination of modeling and experimenting results is expected to reveal the best stimulus waveform and stimulation technique for each neuroprosthetic application in terms of the maximum neurophysiologic response with minimum required battery power.

Tongue Drive: A Tongue Operated Magnetic Sensor Based Wireless Assistive Technology for People with Severe Disabilities

Maysam Ghovanloo and Xueliang Huo

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

Assistive technologies are critical for people with severe disabilities to lead a self-supportive independent life. Persons severely disabled as a result of causes ranging from traumatic brain and spinal cord injuries (SCI) to stroke generally find it extremely difficult to carry out everyday tasks without continuous help. In the United Stated alone, 11,000 cases of severe SCI as a result of automotive accidents, acts of violence, and falls add every year to a population of a quarter of a million. Assistive technologies that help severely disabled individuals such as quadriplegics communicate their intentions to others and effectively control their environment, especially enable them to operate a personal computer (PC), would greatly improve the quality of life for this group of people. These technologies would also ease the individuals' need for receiving continuous help, thus releasing a family member or dedicated care giver(s). They may also help the individuals to be employed and productive in the society.

We are developing an oral tongue-controlled assistive technology, called "Tongue Drive", for control of the environment by severely disabled individuals. The tongue is considered an excellent appendage in many quadriplegics for operating an assistive device. The system will consist of an array of Hall-effect magnetic sensors attached on the outside of the teeth on a dental retainer to measure the magnetic field of a small magnet inside a biocompatible gold or platinum fixture, pierced or implanted and secured on the tongue. The sensor signals will be multiplexed, digitized, and transmitted wirelessly to an external portable computing device such as a pocket computer or personal digital assistant (PDA). The received sensor data is processed to determine the coordinates and relative motion of the tongue with respect to the array of sensors in real time. This information is then used to control the movements of a cursor on a PDA/PC screen. It could as well be used to operate a wheelchair, a phone, home appliances, or other equipments by reconfiguring the software and hardware interfaces. The principal advantage of the Tongue Drive technology is that a few sensors and an inherently wireless small permanent magnet can capture an unlimited number of tongue movements, each of which can represent a specific command. A set of specific tongue movements can be tailored for each individual user and mapped onto a set of customized functions, based on his/her oral anatomy, lifestyle, and disabilities for environment control. Tongue Drive thus provides individuals, who have minimum movement ability, with proportional control of their environments.

The ultimate goal of this project is to develop a mouthpiece, incorporated with an array of sensors, miniature integrated electronics, wireless transceiver, and antenna, powered by small batteries, all fitted inside the mouth. The mouthpiece wirelessly communicates with the PDA, and the PDA, equipped with Bluetooth or Wi-Fi, wirelessly controls the users' environment especially the movement of the mouse cursor on a nearby computer screen. After completion of the hardware and software we are going to conduct actual test and assessment routines by the end users (such as quadriplegics) under supervision of the rehabilitation professionals at the WakeMed Rehabilitation Hospital in Raleigh, NC.

A Wideband Analog Simultaneous 15-Channel Implantable Neural Recording System

Ming Yin and Maysam Ghovanloo
Department of Electrical and Computer Engineering, North Carolina State University, Raleigh, NC

Simultaneous wireless recording of the neural signals from a large number of recording sites is highly desired because a growing number of neuroscientists are interested in visualizing the extracellular activities of hundreds to thousands of single neurons in awake, freely moving animals for behavioral studies. High site-count neural recording systems are currently hardwired. The wires attached to implanted electrodes add noise to the recorded signals and their tethering effects interfere with natural animal behavior, biasing the overall results.

Several multichannel wireless recording systems that have been reported or currently under development use on-chip data reduction techniques such as spike detection to cope with the limited wireless link bandwidth that is the bottleneck in achieving larger number of sites. Even though these techniques are probably useful in some neuroprosthetic applications, they discard useful information such as local field potentials that many neuroscientist are interested in for their research purposes. In addition, the on-chip digital circuits required to perform these functions as well as analog to digital conversion (ADC) contaminate the recorded neural signal through conductive silicon substrate and result in severe signal to noise degradation.

Considering the above problems, we are developing a 15-channel wireless implantable neural recording (WINeR) system that can wirelessly deliver all the information received from the neural tissue in 0.1 Hz ~ 10 kHz range through 15 simultaneous recording sites to the external part of the system. Another major difference between the WINeR and previously reported systems is that the signal path in WINeR is entirely analog and therefore, there is no running digital clock on-chip to interfere with the recorded neural signals. Further, elimination of the ADC and DSP blocks have resulted in saving power consumption and chip realestate on the implant where they are scarce, potentially leading to significant size reduction.

The interfacing between the WINeR system and the neural tissue can be formed by a group of metal microwire electrodes or a micromachined silicon microelectrode array. For every recording channel, a low-noise low-power amplifier (LNA) amplifies the acquired neural signals. A capacitive highpass 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. 15 identical neural recording channels plus a constant reference voltage (MARK) that marks the beginning of each frame are time division multiplexed (TDM) by a 16:1 multiplexer that is controlled by an analog timer. The timer takes 20k samples/sec from every channel, which is enough for reconstruction of the neural signals. A sample and hold (S&H) circuit follows the TDM to stabilize the acquired samples before pulse width modulation (PWM). The PWM block converts the analog signal at the output of the S&H to a pseudo-digital signal that is robust against noise. Finally, a voltage controlled oscillator (VCO) converts the PWM signal to a frequency shift keyed (FSK) RF carrier in the industrial, scientific, and medical band.

A wideband RF receiver is being used as the external part of the WINeR system. The received FSK-PWM signal is directly converted to digitized samples using a high frequency counter. Then by demultiplexing the TDM samples using MARK, the original neural signals are reconstructed. The first prototype WINeR system has been implemented in the AMI 0.5-µm process and is currently under test.

A Wideband Power-Efficient 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 from the external world to implantable biomedical devices with strict size constraints or high power consumption such as neuromuscular stimulators, cochlear implants, and visual prostheses. These devices are either battery-less and should be continuously powered, or have miniature rechargeable batteries that should be inductively charged on a regular basis, without overheating the surrounding tissue or surpassing the exposure limit to electromagnetic field. 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, site impedance measurement, and recording the neural response for accurate electrode placement and parameter adjustments. Therefore, high power transmission efficiency, high data transmission bandwidth, 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 through accurate design, they have not been achieved concurrently with traditional design techniques.

We are developing a wideband power-efficient wireless link for implantable biomedical devices using multiple carriers. In this method, two separate pairs of coils have been utilized for inductive power and forward data transmission through individual carriers. A back telemetry link is also established for reverse data transmission with a pair of patch antennas in the Industrial-Scientific-Medical (ISM) band. We are using three carrier signals at three different frequencies and amplitude levels: (a) low-frequency high-amplitude (f_P < 1MHz, V_P > 50V) for power transmission, (b) medium-frequency medium-amplitude (f_{FD} = 10~100MHz, V_{FD} < 10V) for forward data link, and (c) high-frequency low-amplitude (f_{BT} > 0.5GHz, V_{BT} < 3V) for back telemetry. These carriers 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. Our goal is to achieve high power efficiency and high data bandwidth in both directions. The major challenge is to minimize the interference among multiple carriers especially on the implantable side, where size and power are highly limited. The planar power coils are spiral shaped, and optimized in size to provide maximum coupling coefficient. The data coils are designed rectangular and wound across the power coils diameter. These coils are oriented in parallel in one plane that is perpendicular to the parallel power coil planes in order to maximize their direct coupling, while minimizing their cross-coupling with the power coils.

We have fabricated several coil pairs with optimized geometries obtained through 3-dimensional electromagnetic modeling. Our measurement results are in close agreement with our modeling and simulation results. We are currently in the process of using the developed wireless link to operate a multichannel wireless integrated microstimulating system after which we will move on to *in vitro* and *in vivo* experiments.

Braided Composite Design Strategies for Multielectrode Recording Probes

Simon Giszter1, Ubong Ime Udoewkere2, Heejae Yang3 and Frank Ko3

1. Drexel University College of Medicine,
2. Drexel School of Biomedical Engineering and Health Sciences, and
3. Drexel Department of Materials Engineering, Drexel University, Philadelphia PA 19129.

Wiring and connectors form a major issue in neuroprosthetic design and engineering more generally. Wires' and implant's mechanical impedances, wire tangling, and the consequent stresses on neural tissues and at wire joints and junctions are potentially a major source of failure and neural damage. As current neuroprosthetic designs become more mainstream in clinical application, and as they are applied in more active individuals, the mechanical environment to which neuroprosthetics are subject will likely become increasingly challenging and issues associated with impedance mismatch will become increasingly prominent.

We have been exploring braided designs and fabrication of microelectrodes. Braiding in technology is a means of building strong and flexible stranded and fibrous structures. As an approach to constructing materials it is of ancient pedigree, probably stretching back to the Paleolithic. Braids are made from various topologies of interwoven strands. The mechanical properties of precisely braided composites offer several advantages that are presently utilized in textiles and modern composite materials (in e.g., various sports equipment and body armor). Recently it became clear to our two collaborating laboratories (Giszter and Ko) that these properties were not being similarly exploited for electrode construction on a microscale, most notably for neuroprosthetics in either the central nervous system (CNS) or the peripheral nervous system (PNS). Today, microscale wires and nanoscale fibrous materials can conceivably be braided into composites of a range of mechanical, electrical and biological properties. Braids thus offer a number of potential advantages for electrode construction for neuroprosthetics. The relatively complex structural topologies of braids and the mechanical properties that result from these may have advantages for building electrodes compared to 'conventional' lithography-based more homogenous structures. Braids are self stabilizing structures which can be designed with either low or high compliance, or can be designed to transition back and forth between 'jammed', or stiff, and 'unjammed', or compliant states during manipulation over a supporting form.

The composites we plan will include vicryl and other organics. These will allow composites in which parts of the forming material can provide desirable short term mechanical or bioactive properties and later dissolve, degrade or be physically removed in-vivo to enable more compliant floating electrode implantations.

We present several differing design strategies for braided microelectrode fabrication. We discuss the interaction of fabrication tools, topology and materials properties. Some of our designs are now being tested in vivo, some are being prototyped and some remain designs under development.

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Electrostatic Potential Mapping and Spatial Resolution at the Visual Prosthesis/Vitreous Humor Interface

Elias Greenbaum and Charlene A. Sanders
Oak Ridge National Laboratory, Oak Ridge, TN, USA

Visual prosthesis microelectrode arrays, implanted on the retinas of photoreceptor impaired patients, transfer patterned electrical stimuli across the electrode/vitreous humor interface to the visual neural pathway. To be effective, electrodes must transfer enough charge through the vitreous to exceed neuronal depolarization threshold potentials. However, physiological considerations of safe stimulation restrict the maximum charge density that may be applied to individual electrodes in the array. Decreasing electrode areas and increasing electrode numbers in the newer designs of multipixel prosthesis arrays necessitate investigation of the distribution of interfacial potentials over the active surface of individual and clustered, energized electrodes.

Electric field potentials were mapped above single Pt electrodes and multiple (16X Pt and 60X gold) electrode arrays. Test electrodes were immersed in physiological electrolyte medium. The three-electrode test circuit configuration consisted of a stimulating electrode, a 10 μm recording electrode, and a counter electrode, energized by a stimulus from a pulse generator. The recording electrode was mounted on a xyz translation stage and moved incrementally vertically and horizontally over the stimulating electrode. Pulses were monophasic or symmetrical biphasic, applied at a maximum charge density of 1 mC/cm^2. Voltage between the stimulating and counter electrode (compliance V) and between the recording electrode and counter electrode was monitored on a digital oscilloscope.

Three-dimensional potential maps were generated over the single stimulating electrode as the recording electrode was moved in xyz coordinates over its surface. Voltages in the horizontal plane decreased on either side of the center of the stimulation electrode. Voltages decreased as the vertical distance between the stimulation and recording electrode increased.

Potential profiles over multielectrode arrays were obtained by fixing the position of the recording electrode over an electrode in the center of the array while individually stimulating other electrodes in its vicinity. Potentials from active nearest neighbor electrodes propagated a potential over the center electrode half as high as the voltage from the active electrode. Activation of the next concentric layer of closest electrodes dropped the potential over the center electrode to a third. Cross-talk was higher when track lines of distant activated disks ran next to the center recording electrode.

Potential mapping above single prosthesis electrodes is useful for quantifying the charge from a point source and its propagation through a conductive medium. In multielectrode arrays, the spatial arrangement of electrode disks, their size and pitch, and the metal tracks running between the disks determine the potential profile over the surface of individual electrodes.

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Uncovering the Network Effects of Therapeutic Deep Brain Stimulation

Philip J. Hahn[1], Svjetlana Miocinovic[1,2], Gary S. Russo[3], Weidong Xu[3], Jerrold L. Vitek[3], Cameron C. McIntyre[1,2]
[1]Dept of Biomedical Engineering, Cleveland Clinic, Cleveland, OH
[2]Dept of Biomedical Engineering, Case Western Reserve University, Cleveland, OH
[3]Dept of Neurosciences, Cleveland Clinic, Cleveland, OH

Substantial controversy surrounds the importance of rate, pattern, and synchronization of neural activity in the basal ganglia (BG) network in relation to Parkinson's disease and deep brain stimulation (DBS). We attempted to address some of these issues with the coupled analysis of neural recording data from two parkinsonian non-human primates implanted with scaled down DBS systems and detailed computer models of DBS of the BG network. In previous publications we theoretically and experimentally quantified the neural activity generated at the single cell level during DBS in the region of the subthalamic nucleus in the two monkeys. The fundamental goal of this study was to address the BG network interactions induced by that stimulation. We quantified and compared our experimental single unit recordings from globus pallidus externus and internus (GPe and GPi) before and during high frequency stimulation, evaluating differences between therapeutically ineffective and effective voltage levels. Both ineffective and effective stimulation produced statistically significant increases or decreases in a wide range of neuronal activity characteristics at the single cell level (e.g. interspike interval, interburst interval, percentage of spikes in bursts, percentage of time in bursts, etc.); but no characteristic changed uniformly in every cell. Overall, however, GPi cells exhibited a significant decrease in burstiness while GPe cells exhibited a significant increase in rate when comparing the transition from ineffective to effective stimulation. These experimentally recorded phenomena were reproduced in a large-scale model of the subthalamopallidal network. Our network model was developed using a stochastic description of cortical and striatal inputs to the BG and their relation to beta rhythms from cortical local field potentials. The BG network model exhibited individual spike trains with a statistical description that compared well with *in vivo* recordings from non-human primates. We applied our theoretical predictions of the nonhomogeneous effects of DBS within the complex anatomy surrounding the electrode, and the network model generated shifts in the rate and pattern of network activity consistent with our experimental observations. In addition, the network model allowed us to examine the shifts in rate and pattern across the entire network simultaneously. Our results suggest that therapeutic stimulation decreases abnormal bursting and simultaneously reduces synchronization in pallidofugal activity.

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EMG-Based Control for Upper Extremity Neuroprosthesis

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

Dept. of Biomedical Engineering, Case Western Reserve University
Cleveland FES Center

Contact: juan.hincapie@case.edu

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, the individual 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 arm. 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. The controller was developed using Simulink and xPC-target toolboxes from Matlab software and was implemented as a real-time system using a single board computer.

This work was funded by NIH contract #N01-NS-1-2333

Topics → Models and Stimulation Paradigms; Neural Prosthesis; Sensory/Motor and Functional Neural Stimulation;

Characterizations of PECVD a-SiC_x:H and Parylene Films as an Encapsulation for Chronic Neural Interface Devices

Jui-Mei Hsu [1], Loren Rieth [1,2], Sascha Kammer [3], Chola V.Alluri [4], Prashant Tathireddy [2], Klaus Peter Koch [3], Richard A. Normann [5], Florian Solzbacher [1, 2, 5]

[1] Department of Material Science and Engineering, University of Utah, SLC, UT
[2] Department of Electrical Engineering, University of Utah, SLC, UT
[3] Fraunhofer Institute for Biomedical Engineering IBMT, Germany
[4] Department of Mechanical Engineering, University of Utah, SLC, UT
[5] Department of Bioengineering, University of Utah, SLC, UT

A fully integrated, wireless neural interface device requires a hermetic, biocompatible encapsulation layer at the interface between the device and the neural tissue to maintain long-term recording/stimulating performance. Hydrogenated amorphous silicon carbide (a-SiC_x:H), Parylene C films and a combination of both materials were investigated as encapsulation for such devices.

PECVD was used to deposit a-SiC_x:H film under a deposition pressure of 0.4 Torr and substrate temperature of 150-275˚C. SiH_4 and CH_4 were the precursor gases diluted in hydrogen, and the dilution ratio (hydrogen/precursor) ranged from 0.36 to 12.85 in this work. FT-IR results suggest that deposition conditions with higher hydrogen dilution, higher temperature, and low silane flow typically result in higher Si-C bond density. Silicon substrates deposited with a-SiC_x:H films were placed in 90˚C PBS (phosphate buffered saline) solution for dissolution tests. Elliposmetry studies indicate that no dissolution of a-SiC_x:H films occurred during 6-week measurements. From Impedance spectroscopy (50mV AC) measurement, it was observed that the impedance of 0.7 μm thick a-SiC_x:H film was consistently greater than 10^8 Ohms at 1 Hz over a 4 month period. This result indicates that a-SiC_x:H has a promising encapsulation capability.

In order to study thermal degradation during wire bonding process, Utah electrode arrays (UEA) were coated with Parylene and kept in a saline agar gel to measure impedance of individual electrodes. The impedances were compared after various heat conditions to investigate the thermal impact. Combining a-SiC_x:H and Parylene to further improve encapsulation was studied using a 90˚ peel adhesion test. The test showed Parylene adheres very well to the a-SiC_x:H surface, provided an oxygen plasma and a silane primer were sequentially applied to the surface prior to Parylene coating. Coating conformity of the a-SiC_x:H and Parylene in UEA was evaluated by SEM and optical microscope. The reactive ion etching process for etching of both a-SiC_x:H and Parylene films was investigated, allowing efficient de-insulation of the UEA tips. A double layer encapsulation combining 0.75 μm a-SiC:H and 3 μm Parylene was subjected to a leakage current tests at high bias (5V DC). The leakage current was lower than 10^{-11} A over a period of one month, and remained lower than 10^{-8} A for additional one month.

To summarize, a-SiC_x:H and/or Parylene show conformity and good dielectric-barrier characteristics to hermetically encapsulate the biomedical devices.

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Chronic Analysis of Stimulation of the Recurrent Laryngeal Nerves To Reduce Aspiration

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

1) Dept. of Biomedical Engineering, Case Western Reserve University
2) St. Vincent's Charity Hospital
3) Cleveland VA Medical Center

Aspiration is defined as 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. Previous experiments have shown recurrent laryngeal nerve (RLN) stimulation causes vocal cord closure and reduces aspiration. The recruitment pattern of RLN stimulation has been shown acutely, its chronic stability is now being assessed. To optimize stimulation, we need to understand the correlation between the muscle recruitment and vocal cord closing pressure. We hypothesize that EMG recruitment will not change over 3 months and that the increasing recruitment of vocal fold adductor muscles will cause an increase in glottal closing pressure.

Five dogs are to be implanted for 3 months. EMG electrodes are implanted in the eight intrinsic larynx muscles and a balloon pressure transducer is introduced between the vocal folds. Any systemic effects of stimulation are evaluated by monitoring subject vitals. Following the implant period, tissue is harvested for histology. Two configurations of stimulation are evaluated: a non-cuffed electrode placed in the proximity of the RLN, and a helical cuff electrode wrapped around the RLN.

Stimulation of the RLN causes vocal fold closure. Thresholds between the two different BION systems are 25 nC and 55 nC, leaded and non-leaded respectively. During pulse width modulation, the thyroarytenoid muscles in the larynx are first to be recruited with lateral and posterior cricoarytenoids next. Maximal vocal fold closing pressure is around 120 cm H_2O and pressure recruitment curves correlate with EMG recruitment curves. Bilateral stimulation produces higher closing pressure than unilaterally stimulation but it is not linearly additive. Utilizing the non-leaded BIONs, high stimulation parameters recruit external muscles surrounding the nerve, an adverse effect that can be harmful.

Four dogs have been perfused following the implant period. Tissue has been recovered for histological analysis. No gross tissue response has been seen and the encapsulation tissue is fairly small. Both BION systems did not migrate significantly during the implant period, however routing of the leads of the leaded BION system is important, too superficial of a route results to poor healing of the incision area.

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Protein Functionalized Biomimetic Hydrogel Surfaces for Directing Neural Cell Growth and Attachment

Matthew R. Hynd, John P. Frampton, Natalie Dowell-Mesfin, James N. Turner, William Shain

Wadsworth Center, New York State Department of Health

Albany, New York

Critical to the development of patterned neural networks is the ability to control the spatial localization of molecules on biocompatible materials. Hydrogels are a class of synthetic, non-toxic, hydrophilic polymers used in various biomedical applications. We present here a simple and convenient methodology for the immobilization of proteins onto a biocompatible hydrogel surface to direct neural cell growth and attachment. Hydrogels were formed by long-wavelength UV radiation co-polymerization of an aqueous solution of acrylamide, poly(ethylene glycol) diacrylate and streptavidin-acrylamide. The result was planar, functionalized surfaces of the streptavidin protein capable of binding biotin-labelled biomolecules. The extracellular matrix proteins, fibronectin and laminin, along with the laminin epitope IKVAV, were biotinylated and patterned onto hydrogel surfaces using soft lithographic techniques. Microcontact printing ($\leq$ CP) uses the relief pattern on the surface of an elastomeric stamp to deposit a molecule into a specific pattern on a surface. The stamp is "inked" with the desired solution and brought into contact with the surface. The molecule(s) of interest are only patterned where the stamp is in focal contact with the surface. In order to cast stamps, masters were prepared using four-inch silicon wafers. Wafers were coated with photoresist and ultraviolet (UV)-irradiated through a lithographic mask containing the desired pattern. From this silicon master pattern, complementary elastomeric polydimethylsiloxane (PDMS) stamps were patterned. Briefly, PDMS elastomer was mixed in a 10:1 ratio (elastomer:curing agent), degassed, poured over the silicon master pattern and cured for 2 hours at 60°C. The stamp was peeled away from the master pattern and diced into $1cm^3$ cubes, with each stamp containing one copy of the master pattern. Proteins were patterned using PDMS stamps with relief patterns corresponding to either $10 \leq$ m-wide relief structures and $90 \leq$ m gap spacings or orthogonal $2 \leq$ m-wide

lines connecting a 15 ≤ m diameter node, with a repeat spacing of 50 ≤ m. As a biological assay, LRM55 astroglioma and primary rat hippocampal neurons cells were plated on stamped hydrogels. Both cell types were found to selectively adhere to areas stamped with biotin-conjugated proteins only. Our results demonstrate that hydrogel surfaces can be patterned with multiple proteins and protein epitopes to direct neural cell attachment and growth. This technique may be used to modify fabricated prosthetic devices to enhance biocompatibility.

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Hydrogels to Promote Neuronal Process Growth Towards Neural Prosthetic Device

S Jhaveri 1, M.R. Hynd 2, C.S. Bjornsson 2, J.N. Turner 2, W. Shain 2, C.K. Ober 1

1 Department of Materials Science and Engineering, Cornell University, Ithaca, NY
2 Wadsworth Center, New York State Department of Health, Albany, NY

Micro-machined silicon neural prosthetic devices are fabricated for recording and stimulating specific nervous system sites. However, the long-term performance of these devices is hindered by reactive cell and tissue responses, associated neuron loss, or increased tissue resistivity and decreased electrode performance. Release of neurotrophins can promote either neuron survival and/or neuron sprouting towards device electrodes thus promoting long-term device performance. To test this hypothesis different 2-hydroxyethyl methacrylate (HEMA) coatings were applied to devices as either uniform coatings or by forming 3-dimensional structures near the device electrode. Uniform coatings were obtained by inserting the devices in pre-gel solution filled polyethylene tubes and forming the coatings on the device by using UV light at 365 nm.The coated device is removed from the tube by heating the tube for a few seconds and then immersing it in acid. Three-dimensional structures of hydrogels were made by using multi-photon lithography. This was accomplished by exposing the pre-gel solution to femtosecond laser pulses having a near IR wavelength and confining the polymerization only in the vicinity of the focal point of the laser. With this method we were able to fabricate hydrogels in the shape of reservoirs or wedges to provide long-term neurotrophin release or to insure structural integrity during insertion, respectively. Impedance measurements demonstrated that uniform device coatings did not significantly compromise device electrode recording. Structural stability of hydrogel coatings and polymers was tested by inserting devices into agar brain phantoms and brain tissue slices. Hydrogels on modified devices were loaded with nerve growth factor (NGF) and released (3, 10, 30 and 100 ng/ml) in primary cultures of dorsal root ganglion cells. Cellular responses were measured using biochemical and biological analyses. Two important results have been obtained after analysis of the data obtained. First, bioactive NGF was released from the gels and second the cellular response (process length) was more robust to release of NGF from hydrogels as compared to bath-applied NGF. Different type of response was seen with different type of coatings which has given us valuable information on optimum rate of release and the right chemistry needed for the most effective cellular response. Results from these experiments have provided us important set of conditions for preparing neurotrophin-doped devices for insertion experiments in rat cortex.

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Topic Area: Materials and Devices
Platform Presentation: Yes

Spatiotemporal Neurochemical and Electrophysiological Recordings in Rodents

Matthew D. Johnson[1], Matthew D. Gibson[1], Luis G. Salas[1], Robert K. Franklin[2,3], Richard B. Brown[3], and Daryl R. Kipke[1,2]

[1]*Dept. of Biomedical Engineering, University of Michigan, Ann Arbor, MI*
[2]*Dept. of Electrical Engineering, University of Michigan, Ann Arbor, MI*
[3]*Dept of Electrical Engineering, University of Utah, Salt Lake City, UT*

Since neurological disorders involve modulation of both electrical and chemical activity, monitoring both types of signals may provide unique insights into the underlying pathological mechanisms as well as data to support certain therapeutic approaches. While microelectrodes are reasonably well developed for many electrophysiological measurements, and chemical sensors and delivery systems are in active development, there is a notable paucity of integrated microdevices that can establish concurrent multi-site chemical and electrical interfaces to the CNS with high spatial (μm) and temporal (ms) precision.

We have developed a series of microfabricated silicon-substrate and polyimide-substrate neural probes, which contain proximal microelectrodes for neurochemical and electrophysiological recordings. Prior to use, neurochemical recording sites are coated with membranes and enzyme solutions to facilitate selective amperometric detection of the desired neurotransmitters. These devices have provided a novel means to investigate neurochemical heterogeneity and its relationship to electrophysiological activity.

Our initial efforts have focused on three systems implicated in neurological disorders: dopamine in the striatum, and choline and serotonin in the prefrontal prelimbic cortex. Our results suggest that neurochemical extra-synaptic efflux dynamics can vary in regions as small as 300 μm. Moreover, stimulation of neurotransmitter releasing fibers leads, in some systems, to pronounced changes in local field potential behavior. We discuss the implications of this technology for both investigating neurological disease models and applying it for closed-loop feedback for neurostimulation therapies.

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Binary Control from EEG:
Using One-Dimensional Features for Higher-Dimensional Control

Turan Kayagil [1, 2] , *Ou Bai, Ph.D.* [2] , *Steven Furlani, B.S.* [2] , *Mark Hallett, M.D.* [2]

[1] *Department of Biomedical Engineering, Duke University, Durham, NC*
[2] *Human Motor Control Section, Medical Neurology Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD*

Electroencephalography (EEG) is an appealing basis for brain-computer interface technology because EEG is non-invasive. However, because EEG signals are spatially blurred and typically have very low signal-to-noise ratios, extracting relevant information in the single-event case is challenging. The most easily accessible information is one-dimensional (for example, mu rhythm amplitude, average hemispherical power, or presence of a P300 evoked potential). Many studies have attempted to use such one-dimensional parameters as a basis for control. Robust results may be obtained when control is restricted to answering "yes" or "no" questions, such as comparison of a value to a threshold. However, possible applications of such control have been limited, and more dimensions of control are desirable.

This research presents a new technique for obtaining more dimensions of control from existing technology. Yes/no answers are taken sequentially in groups of n, and in combination designate a specific choice from 2^n possible values. This is homologous to the function of bits, and consequently has been termed "binary control."

To demonstrate this approach, a two-dimensional cursor control paradigm was developed in Matlab. Users move a cursor among squares of a grid towards a target while avoiding a trap. At each move, there are up to four positions into which the cursor may be directed (up, down, left, and right). In this embodiment, control is achieved by twice comparing average alpha- and beta-frequency power of each hemisphere during continuous imagined lateralized hand movement. The first comparison narrows the four choices to two, and the second uniquely determines the cursor movement. This paradigm was shown to be compatible with the Brain-Computer Interface-to-Virtual Reality (BCI2VR) software, and preliminary tests were run on normal volunteers. These tests demonstrated the feasibility of pursuing future research with binary control.

Binary control is promising because of its robust underlying principles, and because it is easily expandable and adaptable. The source of control may be any EEG feature that can signal a yes/no answer, and the quantity of possible choices doubles with the addition of each answer "bit." This might provide means for more complex control, such as of a robotic arm or virtual keyboard. The binary approach might also prove more efficient than current EEG-based control methods, possibly with less computational demand.

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Recognizing speech patterns from Broca's area using the Neurotrophic Electrode in a locked-in subject.

P.R.Kennedy[1.], Siebert, S[1.]., D. Andreasen[1,2.], E.J.Wright[1]. 1: Neural Signals Inc., 3688 Clearview Avenue, S110, Atlanta, GA 30340; 2: Georgia Institute of Technology, Atlanta, GA 30322.

We have restored simple phonemes and syllables to a 24 years old locked-in man with a brainstem stroke and are attempting to produce simple conversational speech. MRI showed anatomically intact hemispheres and functional MRI demonstrated an intact Broca's area during a naming task. We implanted his Broca's area with a two-channel Neurotrophic Electrode with associated twin amplifiers and FM transmitters powered transcutaneously by an induction coil. The sorted single units are fed into a Neural Net for recognizing firing patterns.

Recordings continue to produce 18 single units since early 2005 that are recognized by the Support Vector Machine Neural NET (SVM NN) as related to 32 of the 39 English phonemes. We previously presented initial maps of these phoneme-to-unit firings. We derived these maps by having the subject listen to the phoneme and then he attempted to say the phoneme in his head. Firings of single units were fed back to him as musical notes.

Presently, we are attempting to have him listen briefly to the phoneme, syllable or short word (i, o, u, ma, da, yes, no) and then say it in his head. The firing rates of the 18 single units are fed into the SVM NN offline and firings of units from subsequent sessions are used to build the SVM NN. This robust SVM NN is used online for recognition of the pattern of neural signal firings. The SVM aurally produces the phoneme it recognizes. Presently, the system can recognize these sounds above chance. These studies are ongoing.

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AN IMPLANTED MYOELECTRICALLY-CONTROLLED UPPER EXTREMITY NEUROPROSTHESIS

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

1) MetroHealth Medical Center,
2) Case Western Reserve University
3) Cleveland VA Medical Center
Cleveland, Ohio

A second generation implantable neuroprosthesis has been developed which provides improved control of grasp-release, forearm pronation, and elbow extension for individuals with cervical level spinal cord injury. In addition to the capacity to stimulate twelve muscles, the key technological feature of this advanced system is the capability to transmit data out of the body. This allows the use of myoelectric signal recording via implanted electrodes, thus minimizing the external components required for system use. Clinical studies have been initiated with this second generation neuroprosthesis. The specific components of the system are: twelve stimulating electrodes, two myoelectric signal recording electrodes, an implanted stimulator-telemeter device and an external control unit and transmit/receive coil. This system has been implemented in ten arms in seven C5/C6 spinal cord injured individuals. The longest time post implant is now three years. Three subjects have two devices implanted, one in each arm for bilateral function. Myoelectric recording electrodes are typically placed on one voluntary forearm muscle, usually the extensor carpi radialis longus, and one neck muscle, usually trapezius or platysma. The myoelectric signal from the wrist extensor is used to proportionally control grasp opening and closing, while the signal from the neck is used to lock and unlock the hand grasp and to switch between grasp patterns. Functional systems have been successfully implemented with all subjects. All subjects have demonstrated increased pinch force and improved grasp ability. All subjects have demonstrated increased independence and improved function in activities of daily living. Tasks in which subjects demonstrated improvement include: eating with a fork, drinking from a glass, writing, brushing teeth, brushing hair and applying lip gloss. Bilateral users have demonstrated the ability to open jar lids and cut food. There have been no technical issues with the implanted components and no implant-related medical issues. Three of the twenty myoelectric recording electrodes have been relocated in a subsequent procedure in order to obtain improved signal quality. The use of myoelectric signals as a control sources have been extremely successful. The results from these subjects demonstrate that myoelectric signals can be recorded from voluntary muscles in the presence of electrical stimulation of nearby muscles. Subjects can learn to use the myoelectric signal as a proportional control signal and as an on/off signal. We believe that these results indicate that implanted myoelectric recording is a desirable control option for neuroprostheses.

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Nerve Conduction Block Utilizing High Frequency Alternating Current

Kevin L. Kilgore[1,2,3], Niloy Bhadra[2], Emily A. Lahowetz[2], J. Douglas Miles[4]

1) MetroHealth Medical Center,
2) Case Western Reserve University
3) Cleveland VA Medical Center
4) University Hospitals of Cleveland
Cleveland, Ohio

High frequency alternating current (HFAC) can block conduction in mammalian peripheral nerves when delivered through nerve cuff electrodes. We have demonstrated that alternating current in the frequency range of 10 kHz to 30 kHz can produce a repeatable, gradable and reversible nerve conduction block. The block produced by HFAC can achieve 100% effectiveness within tens of milliseconds. The block can be maintained as long as the HFAC is delivered, and then can be completely reversed in less than a second by turning the HFAC off. It is possible to modulate the block so that only a percentage of the fibers in the target nerve are blocked. These features make HFAC nerve block a unique tool with considerable potential for the treatment of muscle spasticity and pain in humans.

At present, two major roadblocks prevent the use of HFAC block in human applications. First, HFAC produces a brief period of intense activity in the nerve when it is first turned on. This "onset response" can vary from a single action potential to prolonged activity lasting tens of seconds. For most clinical applications, it is necessary to eliminate this response before HFAC block can be practically applied. Second, the chronic safety of HFAC block to whole nerves has not been demonstrated. We are seeking solutions to these issues so that testing of HFAC block in humans can proceed.

Potential solutions to eliminating the onset response involve transitory modifications of the HFAC waveform so that the onset activity does not escape the cuff electrode and travel along the nerve. By coupling a short duration block using direct current with the HFAC block, it is possible to achieve block without the onset response. Although long-term delivery of direct current would be damaging to both the tissue and the electrode, the tissue may be capable of buffering the low-level short duration direct current that would be necessary to eliminate the onset activity.

A chronic test of HFAC block was performed in six dogs. HFAC block was delivered to the radial nerve for 15 minutes twice a week for five weeks. There was no evidence of demyelination or damage to the nerve within the blocking cuff. Activation thresholds taken from the nerve at the time of implant and explant did not show any significant difference. This provides the first preliminary evidence for the safety of HFAC waveforms when applied for brief periods.

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Numerical Study of Thermal Impact of the 3-D Microelectrodes Array Implanted in the Brain

Sohee Kim[1], Richard A. Normann[2], Reid Harrison[1], Florian Solzbacher[1,2]

[1] *Department of Electrical Engineering, University of Utah, SLC, UT*
[2] *Department of Bioengineering, University of Utah, SLC, UT*

Towards a chronically implantable, wireless neural interface device, it is required to integrate a power source and electronics circuitry with the microelectrodes array. Since the electronics IC dissipates a certain amount of power while it amplifies detected neural signals, processes and transmits them to an extracorporeal receiver, it will affect the temperature in surrounding tissues where it is implanted. To the authors' knowledge, there are no studies addressing thermal effects of the implantation of a 3-dimensional microelectrode array. We investigate this thermal aspect of the neural interface using numerical method as the first step towards *in vivo* thermal evaluation of the recording or stimulating electrodes arrays.

In this study, thermal impact of the integrated 3-D Utah Electrode Array (UEA) implanted in the brain was investigated through simulations using finite element analysis (FEA). Only heat transfer in conduction was taken into account, since conduction is the most important mechanism of heat transfer within biomaterials. Convection through blood flow, which in effect cools down the tissue temperature, was not considered for this preliminary study. Thus, the observations by using this modelling can be considered as the upper boundary of possible temperature increases. The tissues of interest were assumed to be homogeneous and isotropic. The integrated UEA with the IC chip was modelled in a 3-D Cartesian coordinate.

From the simulation, temperature increase of 1.2 °C was observed in steady state for the chip dissipating 13 mW. To validate the modelling and method used for simulation, a simple *in vitro* experiment was performed using an electrical resistor as a substitute of the IC chip and agar gel for the brain tissue. Spatial temperature distribution was detected using an infrared thermal camera. Temperature increases observed from measurement and simulation were in good agreement. In the future, we are planning on monitoring temperature of the neural interface while recording, using an on-chip temperature sensor. This will provide a reliable reference to validate the heat model and simulation proposed here and further allow monitoring the temperature of the neural interface during operation.

We will present the simulation method and modeling used to predict the thermal impact of an implanted 3-D Utah microelectrode array, simulation results as well as some preliminary experimental data.

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Topic area: Neural Prosthesis

Implanted Upper Extremity Neuroprosthesis in Hemiplegia

Jayme S. Knutson,[1] John Chae,[1,2] Kevin L. Kilgore,[1,2,3] Harry A. Hoyen,[2]
Michael W. Keith,[1,2] P. Hunter Peckham[1,2,3]
[1]*Biomedical Engineering Department, Case Western Reserve University, Cleveland, OH*
[2]*MetroHealth Medical Center, Cleveland, OH*
[3]*Louis Stokes Cleveland Department of Veterans Affairs, Cleveland, OH*

Many stroke survivors never regain function of their hemiparetic upper extremity. An implanted neuroprosthesis has been shown in tetraplegic spinal cord injured subjects to reduce upper extremity impairment, improve hand function, and increase independence in activities of daily living. This project evaluates the feasibility of implementing an implanted neuroprosthesis in stroke survivors and evaluates the effect of the neuroprosthesis on upper extremity motor impairment and activity limitation.

To date, one subject has undergone neuroprosthesis surgery, and is presently in the post-surgical muscle conditioning phase, prior to having her system set up for functional use. A 57 year old female stroke survivor, 3 years post right hemisphere hemorrhagic stroke, presented with paretic hand and elbow extensors preventing hand opening and reach, having shoulder subluxation without pain, some voluntary finger flexion and wrist extension and flexion, and ability to functionally position the hand in the workspace. A screening protocol was used to ensure that she did not have a degree of flexor hypertonia that prevented electrical stimulation of extensors from producing functional hand opening.

On May 16, 2006, this subject became the first stroke patient to receive an implanted upper extremity neuroprosthesis. A 12-channel stimulator-telemeter was surgically implanted in the right upper pectoral region. Stimulating electrodes were implanted in the supraspinatus (to reduce shoulder subluxation), triceps, wrist extensor, and finger and thumb flexors and extensors. This subject's retention of voluntary twitches of the extrinsic finger extensors and activation of the deep finger flexor muscle presented the unique opportunity to attempt to implement a control strategy that may be even more intuitive than previous implementations. EMG-recording electrodes were implanted on the extensor digitorum communis (EDC) and on the flexor digitorum profundus (FDP), with the intention of using EDC activation to trigger extensor stimulation and FDP activation to control flexor stimulation.

The surgical procedure was significantly shorter than our typical experience with spinal cord injured subjects. This was due in large part to the relative ease of identifying optimal electrode positions on muscles that remain fully innervated, which is often not the case in spinal cord injury. The subject tolerated surgery well, and was discharged 3 days later. At 3 weeks post-op, stimulation patterns for exercising her muscles were crafted, and the subject has been using the stimulator at home for 6-8 hours daily for exercise. She will return to the laboratory for system customization and training in July.

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A Novel Functional Electrical Stimulation Therapy for Recovery of Hand Function in Hemiplegia

Jayme S. Knutson,[1] Mary Harley,[2] Terri Hisel,[2] John Chae[1,2]
[1]*Biomedical Engineering Department, Case Western Reserve University, Cleveland, OH*
[2]*Physical Medicine and Rehabilitation, MetroHealth Medical Center, Cleveland, OH*

One of the most frequently persisting consequences of stroke is impaired hand function. The purpose of this research program is to develop neuromuscular electrical stimulation applications that facilitate motor recovery after stroke. This project represents the first clinical test of a unique method of electrically activating hand extensor muscles to promote recovery of voluntary hand opening.

This case series pilot study includes chronic (> 6 months) stroke survivors with upper extremity hemiparesis. Surface electrodes activate finger and thumb extensors to produce hand opening. Subjects control the degree of stimulated hand opening with an instrumented glove worn on the unimpaired hand. The intensity of stimulation to the paretic hand is proportional to the degree of opening of the gloved unimpaired hand. This paradigm places the subject back in control of their paretic hand, and provides a strong coupling between motor intention (central activity) and motor output (peripheral activity). The subjects use the stimulator at home daily and in the laboratory twice a week for 6 weeks. The daily use at home consists of repetitively opening the hand in response to audio cues for a total of 2 hours per day. The laboratory sessions consist of using the stimulator to practice functional tasks with the paretic hand. Upper extremity motor impairment is assessed before and after the intervention period, and at 1 and 3 months thereafter.

Three subjects have participated in the study. Preliminary data analysis comparing one-month follow-up to baseline shows increases in voluntary finger extension range of 30 and 33 degrees for subjects 1 and 3, respectively. Subject 2 had full, but weak, finger extension at baseline. Finger extension tracking accuracy increased for all three subjects by 21 to 73%. Upper extremity Fugl-Meyer Motor Assessment scores increased in each subject by 5 to 15 points (representing 16 to 53% increases). Box and block scores increased in each subject by 6 to 9 points (representing 86 to 900% increases). Each subject also had trends toward increasing finger extension strength.

These preliminary data suggest that contralaterally controlled functional electrical stimulation therapy may be effective in facilitating recovery of hand function in chronic hemiplegia. The effect may be more significant during the acute phase of recovery. A randomized clinical trial is needed to confirm the effect.

This work was supported by the State of Ohio Biomedical Research and Technology Transfer (BRTT) Trust and NIH K12 HD049091.

Scope and Resolution, Simulating Large Scale Neuronal Networks to Study The Effect of Morphological Detail on Emergent Large Scale Patterns of Activity

Randal A. Koene[1,2], Nikos Green[2], Ger Ramakers[2], Jaap van Pelt[2] and Arjen van Ooyen[2]
1 Boston University Center for Memory and Brain
2 The Netherlands Institute for Neuroscience
randalk@minduploading.org

To capture subject specific variation, a neural prosthetic strives to emulate the function of the original neural substrate, rather than a function based on a set of recorded responses to a limited set of input sequences. *Scope:* Subject specific robust functions in the biological substrate are produced by a large number of components. Individual contributions depend on mechanistic detail. The morphology of neurons affects electrical processes in cortical neuronal networks. For example, interaction between activity at synapses located on different parts of a dendritic arbor affects somatic membrane potential. Clinical evidence reveals that genetic or traumatic (stroke, disease) abnormalities of morphology can lead to changes in brain activity and behavior. The neural substrate includes self-correcting, redundant and homeostatic processes. *Resolution*: Stable functional relationships are established using detail of biophysical processes.

Computational studies with *sufficient resolution*, detailed processes at the level of neuronal morphology, and *sufficient scope*, the processes of activity in large networks of connected neurons, have been difficult to achieve. We propose a computational framework for the generation of networks consisting of large numbers of neurons with realistic morphology and synaptic connectivity developed according to phenomenological growth models that are inspired by mechanisms of neuronal development.

Unlike previous efforts (Ascoli *et al*., Anatomical Embryology, vol.204, 2001), we explicitly incorporate the temporal aspect of network development by using growth models. Realistic networks are generated at successive stages of development, so that the emergence of characteristic connectivity and spatio-temporal patterns of activity may be understood. This extends previous research that separately addressed the development of individual neuron morphology (van Pelt and Uylings, Brain and Mind, vol.4, 2003) and the dynamic processes in large developing networks (van Ooyen *et al*., Journal of Theoretical Biology, vol.172, 1995).

Neurons of a specific age and type are simulated in two or three dimensions. Morphogenesis applies growth models to axons and dendrites. Models inspired by growth cone mechanisms determine direction and diameter of elongating fiber. Models of synapse formation enable simulation of electrical activity in the networks.

First applications are: (1) Examining emergent connectivity and causes of spatio-temporal patterns of activity in developing networks of rat cortical neurons cultured on a substrate with micro electrode array. (2) Examining patterns of emergent activity in three dimensions, comparing simulations with high-speed optical recording of activity in slices of rat neocortex and hippocampus. (3) Studying competitive processes during neurite development.

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Voltage- and Frequency-Dependent Changes in Tremor Parallel Changes in Neuronal Regularity for Thalamic Deep Brain Stimulation

Alexis M. Kuncel[1], Scott A. Cooper[2], Barbara R. Wolgamuth[2], Warren M. Grill[1]

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

The mechanism(s) by which deep brain stimulation (DBS) alleviates tremor remains unclear, but successful treatment can be achieved with properly selected frequency and voltage. We studied the effects of stimulation frequency and voltage on the clinical tremor response to DBS and the output of a population of intrinsically active model neurons to test the hypothesis that regularization of neuronal firing patterns is responsible for the clinical effectiveness of DBS.

We measured changes in postural tremor in response to 40-80 combinations of frequency and voltage in 14 thalami (9 subjects) with thalamic DBS for essential tremor. The clinical tremor response was dependent on the stimulation frequency and voltage. With high frequency (>100 Hz) stimulation, increasing the amplitude resulted in tremor suppression, until maximum suppression occurred at a critical voltage. Increasing the stimulation amplitude beyond this critical voltage resulted in reduced tremor suppression or exacerbation. Increasing the amplitude of low frequency (< 50 Hz) DBS aggravated tremor.

The regularity of firing across a population of neurons was similarly dependent on stimulation frequency and voltage. One hundred independent model thalamocortical neurons were distributed uniformly within a 3 mm radius sphere, and spike times in the axon were recorded. The neuronal firing patterns were quantified using the mean and standard deviations of the interspike intervals over 200 ms periods, and the coefficient of variation (CV), defined as the standard deviation divided by the mean, was used as a measure of information content of the output. Above a critical stimulation frequency, increasing the stimulation amplitude reduced the population's median output CV, while for low frequencies, increasing the stimulation amplitude resulted in an increase in the population median output CV.

The correlation between the changes in tremor and the changes in the CV of neuronal firing supports the hypothesis that regularization of neuronal firing pattern during DBS is responsible for its clinical effectiveness.

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Electrical Conduction Block of Sensory Nerves

Emily Lahowetz[1], B.S., Niloy Bhadra, M.D., Ph.D.[1], Kevin L. Kilgore, Ph.D.[2]

[1] *Department of Biomedical Engineering, Case Western Reserve University, Cleveland, Ohio*
[2] *Department of Orthopedics, MetroHealth Medical Center, Cleveland, Ohio*

A reversible electrical nerve block has potential clinical benefits in treating pathological neural hyperactivity, such as spasticity, movement disorders, muscle spasms, and chronic pain. It has been shown through computer simulations and in vivo experiments that high frequency alternating currents (HFAC) can be used to produce a quickly reversible, local conduction block along peripheral motor nerves. Although reliable motor block has been demonstrated, little work has been published regarding block of sensory fibers, which would be primarily influential in chronic pain applications. We hypothesize that a reversible, complete conduction block of myelinated sensory nerves can be achieved using HFAC stimulation.

In vivo experiments in a rat sciatic nerve preparation were performed using CAP recordings as an outcome measure to detect conduction block of myelinated sensory fibers. HFAC frequencies between 10kHz and 30kHz were tested at amplitudes ranging from 1Vpp to 10Vpp. Complexities involved with acquiring CAP in the presence of this type of high-amplitude high-frequency waveforms have been identified. Based on what we have learned from our preliminary work, future experiments will involve both CAP and single fiber recordings (SFR) in a rabbit model.

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Computational Approach to Sensorimotor Control of Human Reaching Movements

Dan Song[2], Ning Lan[1] and James Gordon[1]
1. Dept. of Biokinesiology and Physical Therapy
2. Dept. of Biomedical Engineering
University of Southern California
Los Angeles, CA 90089

Abstract

Sensorimotor dynamics and musculoskeletal mechanics present necessary constraints to neural control of motor tasks. We have developed an integrated virtual arm (VA) model that is suitable for computational study of sensorimotor control of reaching movements in human. The VA model has shoulder, elbow and forearm degrees of freedom (DOF), 15 virtual muscles^{TM} (VM) acting at these joints, a spindle sensor and a Golgi Tendon Organ (GTO) sensor embedded in each muscle, and a cascaded model of spinal circuits. Given a set of α and γ commands, the VA model can compute joint kinematics, muscle forces and joint torques, stiffness of the muscle, joint and hand, as well as proprioceptive afferents from spindle and GTO models.

We performed two sets of simulation studies to test the VA model with and without proprioceptive afferents during postural control. In open-loop case, the VA was stabilized at three hand equilibrium positions at different levels of co-activations of three pairs of antagonist muscles. The hand stiffness ellipses obtained from simulation showed the similar features in behavioral human subjects during postural maintenance. When signal dependent noise (SDN) was added to motor commands of muscles, the noise propagated through the neuromuscular system, and excited a random drifting of hand around its equilibrium position. The drifting pattern was determined by the characteristics of hand stiffness ellipse, and was also consistent with the stability nature of the distal and proximal joints of the multi-joint arm. With proprioceptive afferents, a moderate gain of reflexes ensured the stability of the closed-loop system, and a smaller hand drifting was displayed with a smaller hand stiffness ellipse than that of open-loop system. This indicates that proprioceptive feedback improves the efficiency of open-loop system to suppress the effects of motor noise, and that the closed-loop system with moderate reflex gains is sufficiently stable to resist internal disturbances. The results confirm that the VA model is suitable as a test bed for evaluating the biological plausibility of motor control strategies. The VA model could also be modified to understand the pathological behaviors with neurological disorders, such as spinal cord injury and stroke.

Keywords, muscle, spindle, Golgi Tendon Organ (GTO), multi-joint arm, stiffness, postures, reaching movements, modeling and simulation

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ROLE OF ASTROCYTES IN THE MECHANISM OF DEEP BRAIN STIMULATION

Kendall H. Lee 1, Vivianne Tawfik 2, Frederick L. Hitti 3, James C. Leiter 3, and David W. Roberts 4
1 Department of Neurosurgery, Department of Physiology and Biomedical Engineering, Mayo Clinic, Rochester, MN
2 Department of Pharmacology, Dartmouth Medical School, Hanover, NH
3 Department of Physiology, Dartmouth Medical School, Hanover, NH
4 Section of Neurosurgery, Dartmouth-Hitchcock Medical Center, Lebanon, NH

Deep Brain Stimulation has been thought to effect neuronal populations to achieve clinical benefits. However, the effects on astrocytes is yet unknown. In the present study, we investigated the effects of DBS on astrocytes to test the hypothesis that the efficacy of DBS is due to astrocytic modulation of neuronal activity.

Direct measurement of glutamate release was made using a dual enzyme-based electrochemical sensor in the ferret thalamus slice, in vivo rat VL thalamus, and in primary astrocytic cultures. Electrical stimulation (100 microsec pulse width; 1 sec to 60 min pulse duration; 100-2000 microA or 1-20 volt amplitude; 5-1000 Hz frequency) using a bipolar stimulating electrode was given. In addition, intracellular and extracellular electrophysiological recordings were made in the nucleus Reticularis thalami (nRt) and in thalamocortical relay neurons in an in vitro slice preparation from the ferret lateral geniculate nucleus (LGN) that generates spontaneous network oscillations. Fluorescent microscopy was performed using Flou-4 to visualize intracellular calcium release in primary astrocytes cultures.

Stimulation of the thalamus in vivo and in vitro resulted in glutamate release that reached a plateau after ~5 min, and remained elevated for the duration of stimulation. The glutamate release was evoked even in the presence of the Na+ channel blocker tetrodotoxin or in high Mg++, low Ca++ solution. Electrical stimulation of primary astrocyte cultures evoked glutamate release that was quantitatively similar to the glutamate release previously observed in vivo and in vitro. The glutamate release was blocked by bath application of the calcium chelator BAPTA-AM. Bafilomycin A1, a vesicular ATPase inhibitor, bath application eliminated the rise in glutamate release in the ferret thalamic slice. Glutamate amperometric recordings in ferret thalamic slices resulted in local glutamate release, while intracellular recordings revealed that HFS of thalamocortical relay neurons generated excitatory post-synaptic potentials (EPSPs), increased the number of action potentials during the stimulation period, and abolished synchronized oscillations. Fluorescent microscopy revealed increases in intracellular calcium levels in astrocytes that were time locked to HFS.

These results suggest that HFS of the thalamus leads to a calcium dependent vesicular glutamate release from astrocytes that is insensitive to classic neuronal exocytosis inhibitors. Thus, astrocytic glutamate release may be an important mechanism by which

DBS is able to block synchronous neural network oscillatory activities such as those that generate tremor and seizures.

Neuromodulation of the Ventromedial Hypothalamus of the Rat Through deep Brain Simulation Effects Animal Weight

M.J. Lehmkuhle and D.R. Kipke

Dept of Biomedical Engineering, University of Michigan, Ann Arbor, MI, USA

Deep Brain Stimulation

It is estimated that 30% of the adult US population is obese. Over 4 million Americans are considered morbidly obese (clinically severe obese), a serious disease generally defined as weighing 100 pounds or more over ideal body weight. In addition to numerous negative social, psychological, and economic effects, morbid obesity increases the risk of death from diabetes or heart attack and "end-stage" (untreatable) obesity. Evidence in rats suggests that pacing the hypothalamus with deep brain stimulation could have the potential to effectively regulate metabolism.

Here, long-term neuromodulation of the ventromedial hypothalamus (VMH) through deep brain stimulation is assessed for regulating the neural components of metabolism in the rat. Sprague-Dawley and Long-Evans rats (230.3 - 273.6 g or >700 g) were implanted with a single bipolar concentric stimulation electrode (Plastics1, MS-308, 70 - 100 KΩ @ 1 KHz) in the left VMH using stereotaxic coordinates (-2.3 caudal, 0.6 lateral, -9.5 ventral, mm r.e. bregma). Intraoperative electrophysiological recordings revealed tonic firing rates of 1.0 – 5.3 spikes/sec. Animals were continuously stimulated with charge-balanced, biphasic, cathodic-first constant-current pulses, 10 μA, 250μsec/phase (2.5 ηC/phase, 1.2 μC/cm^2), at frequencies of either 150 or 500 Hz for up to six weeks.

It was found that the weight of control animals could be predicted by a 2nd-order relationship with time. Likewise, the weight of animals that were implanted but not stimulated could also be predicted as a function of time, however these animals gained weight at a faster rate in the first week following implantation than non-implanted rats. Animals that were given six weeks of recovery prior to six weeks of electrical stimulation exhibited a consistently linear increase in weight that was dependent upon stimulation frequency; 150 Hz stimulation produced a faster rate of weight gain (4.1x normal) than 500 Hz stimulation (2.2x normal). In all stimulated animals, the efficiency (change in weight / amount of food eaten) did not deviate from control animals, however the amount of food consumed increased by 18% (500 Hz) and 77 % (150 Hz).

These results suggest that electrical stimulation of the VMH is effecting an increase in metabolic function that is being countered by an increase in food consumption. The effects of long-term neuromodulation of the hypothalamus in both young rats and obese rats will be assessed. Neuromodulation of the hypothalamus with deep brain stimulation may provide an effective means to regulate metabolic function.

Theoretical Optimization of Silicon-Substrate Microelectrode Contact Surface Area

Scott F. Lempka[1,2], *Matthew D. Johnson*[3], *David W. Barnett*[4], *Michael A. Moffitt*[5], *Kevin J. Otto*[6], *Daryl R. Kipke*[3], *and Cameron C. McIntyre*[1,2]

[1]*Dept. of Biomedical Engineering, Cleveland Clinic Foundation, Cleveland, OH*
[2]*Dept. of Biomedical Engineering, Case Western Reserve University, Cleveland, OH*
[3]*Dept. of Biomedical Engineering, University of Michigan, Ann Arbor, MI*
[4]*Dept. of Biomedical Engineering, Saint Louis University, St. Louis, MO*
[5]*Advanced Bionics, Sylmar, CA*
[6]*Dept. of Biological Sciences, Purdue University, West Lafayette, IN*

Intracortical microelectrode recordings of neural activity show great promise as control signals for neuroprosthetic applications. However, reliable long-term recording of single unit spiking activity with chronically implanted microelectrode arrays remains challenging. Many approaches seek to enhance the long-term performance of microelectrode arrays by, for example, increasing electrode biocompatibility, decreasing electrode impedance, or improving electrode interface properties through application of small voltage pulses. The purpose of this study was to use computational models to optimize the design of intracortical silicon-substrate microelectrodes. We coupled detailed models of the neural source signal, silicon-substrate microelectrodes, and thermal noise to define the electrode contact size that maximized the signal-to-noise ratio (SNR). The model analysis combined a multi-compartment cable model of a layer V cortical pyramidal neuron with a 3D finite element model of the head and microelectrode to define the amplitude and time course of the recorded neural signal. A spatially-lumped impedance model was parameterized with *in vitro* and *in vivo* spectroscopy data and used to define thermal noise as a function of electrode contact size. Microelectrodes with circular platinum recording sites of 50, 177, 380, 1520, and 2830 μm^2 were examined. Our results suggest that intracortical microelectrodes with a contact size of ~380 μm^2 will maximize SNR *in vivo* and may improve the long-term recording capabilities of silicon-substrate microelectrode arrays.

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

Hilton G. Pryce Lewis, Neeta P. Bansal, and Karen K. Gleason
GVD Corporation, Cambridge MA 02139

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 non-uniform wetting are eliminated, making vapor deposition especially useful for encapsulating objects having features or dimension of less than 100 microns, such 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.

A series of iterative experiments have been used to identify iCVD process conditions that successfully provide electrical insulation to 25 micron 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 are observed in optical or electron micrographs after the flex testing. These iCVD PTFE coatings were demonstrated to have bulk surface resistivity greater than 10x 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.

In the Phase II, GVD will expand the use of thin iCVD PTFE coatings for insulating and protecting neural probe assemblies. A new coating system has been designed and built that is capable of coating sufficient numbers of prototypes for testing, optimization of the process for coating 3D substrates, and further research into adhesion promotion strategies for the substrates of interest and long term testing of the coating's biocompatibility.

At the end of this Phase II work, GVD will be able to offer to researchers and manufacturers a proven, effective solution to the problems of insulation and encapsulation of neuroprosthetic devices. This will enable greater flexibility in the design of these devices, the choice of materials used, and the minimum dimensions which can be achieved. The therapeutic benefit will be to debottleneck the development of these devices and accelerate their proliferation as treatments for neurological disorders.

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Rifampicin-Loaded Silicone: A New Approach to Tuning Release Rate with Self-Assembled Monolayers and Cast Molding

Xuemei Liang[1], Haiying Tang[1], Anfeng Wang[1], Ting Cao[1], Steven O. Salley[1], J. P. (Pat) McAllister II[2], and K. Y. Simon Ng[1]

[1] Department of Chemical Engineering and Materials Science, Wayne State University, Detroit, MI
[2] Department of Neurological Surgery, Wayne State University School of Medicine, Detroit, MI

Providing a longer period of sustained antibiotic release is an important challenge to the development of catheters for long-term implantation, especially for intracranial applications such as diversion of CSF for the treatment of hydrocephalus. This study aimed to evaluate the long-term in vitro drug release performance of cast-molded catheters with self-assembled silane monolayer coatings to provide a tuneable release rate. A cast-molding approach was used to load rifampicin into the silicone precursor prior to curing. Self-assembled perfluorodecyltrichlorosilane (FAS) and octadecyltrichlorosilane (OTS) monolayers and FAS multilayers were deposited on the drug-loaded silicone surface by chemical vapor deposition and molecular vapor deposition, respectively. The morphology of adhered bacteria was observed by scanning electron microscopy and atomic force microscopy. The antibiotic release rate was determined by UV spectrometry. The efficacy of the rifampicin was determined by measurement of Staphylococcus epidermidis adhesion on treated and untreated silicone surfaces using a colony counting method. Cast molding avoided the microstructural changes and minimized the initial "burst effect" compared with the diffusion-controlled technique. Sustained in vitro release from rifampicin-loaded silicone for at least 110 days at approximately 2-4 µg/cm2-day was achieved. The rifampicin-loaded silicone decreased bacterial adherence by 99.8% on fresh 8.3% rifampicin-loaded silicone. FAS multilayers were effective in moderating the burst effect and achieving a longer-term delivery compared with FAS and OTS monolayers. Incorporation of antibiotics into shunt catheters has been accomplished by others. However, the surfactant used in Cook Spectrum catheters to bind minocycline is toxic to nervous tissue, and drug release from BactisealTM catheters is reported to be only 28 days. Combining molecular vapor deposition of FAS or OTS with cast molding impregnation of rifampicin into silicone, we have prolonged drug release well beyond this time. Cast molding can be adapted to a host of pharmacologically active ingredients or combinations and applied to a variety of catheter-based drug release treatments.

Auditory Midbrain Implant: Current Progress and Future Directions

[1]Hubert H. Lim, [1]Minoo Lenarz, [2]Amir Samii, [1]Guenter Reuter, [3]James F. Patrick, [2]Madjid Samii, [1]Thomas Lenarz

[1]Department of Otolaryngology, Medical University of Hannover, Germany
[2]Department of Neurosurgery, International Neuroscience Institute, Hannover, Germany
[3]Cochlear Ltd., Lane Cove, Australia

There is a need for a central auditory prosthesis for deaf patients who do not have viable auditory nerves or implantable cochleae and thus cannot benefit from cochlear implants. This includes patients with neurofibromatosis type II (NF2), which is a genetic disease that occurs in about 1 in 40,000 births. Within the last decade, significant research and clinical efforts have focused on developing and implementing an auditory midbrain implant (AMI) placed into the inferior colliculus central nucleus (ICC) that is now in clinical trials.

A human prototype AMI array was developed in collaboration with Cochlear Ltd. (Lane Cove, Australia). The silicone array consists of 20 platinum electrode rings linearly spanning a distance of about 4 mm. A stainless steel stylet is positioned through the center of the array to enable insertion along the tonotopic gradient of the ICC, and is removed after array placement. The other components of the AMI system are similar to those of the latest Nucleus cochlear implant systems by Cochlear Ltd.

As an initial step, we electrically stimulated different regions within the ICC via the AMI array and recorded the corresponding neural activity within the primary auditory cortex using a multi-site probe in guinea pigs. Our results confirm that stimulation of the ICC via the AMI array can elicit low threshold and frequency-specific cortical activation with current levels that are safe for central nervous system stimulation. Based on a cat model, long-term implantation and stimulation of the AMI array has shown to be safe with minimal glial reaction and no significant neuronal damage. These results demonstrate the potential of the AMI in safely restoring auditory sensations in deaf patients.

Since the first patients are those with NF2, we needed to develop an approach that would enable vestibular schwannoma surgery and then provide sufficient exposure for implanting the AMI array along the tonotopic gradient of the ICC with minimal added risk. Based on simulations in cadaver specimens, these criteria can be achieved using a lateral suboccipital craniotomy to expose the tumor and then extended to a lateral supracerebellar infrantentorial approach to access the inferior colliculus.

These animal and cadaver studies have provided the necessary validation and information to proceed with clinical trials. The preliminary findings in the first implanted AMI patient will be presented and discussed with respect to future directions for AMI research.

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Topic Area: Auditory Prostheses

Gaja Mahadevan

Infrared Laser Pulse-Induced Ventral and Dorsal Root Potentials of Mammalian Spinal Cord – An *In Vivo* Studies

Gajendiran Mahadevan 1, Jonathan D. Wells 1, C. Chris Kao 2, Peter E. Konrad 1, 2, Anita Mahadevan-Jansen 1, 2, E. Duco Jansen 1, 2

1 *Department of Biomedical Engineering, Vanderbilt University, Nashville, TN,*
2 Department of Neurological Surgery, Vanderbilt University, Nashville, TN.

Alternative neural stimulation techniques has been explored over a decade to overcome stimulation artifacts, neuronal damage, difficulties in simultaneous stimulation and recordings, and above all lack of spatial specificity of century old classical electrical stimulation for both central and peripheral nervous systems.

We have stimulated mammalian spinal cord for the first time with low level, pulsed infrared laser light. Present *in vivo* studies, the spinal cord was exposed by dorsal laminectomy at the lumbo-sacral region and the lumbar L4, L5 and L6 dorsal and ventral roots were isolated and exposed on the left side of urethane anesthetized adult Sprague-Dawley rats. The ipsilateral sciatic nerve was also isolated and exposed for peripheral stimulation and recording. The dorsal and ventral roots and sciatic nerves were intact during both electrical and optical stimulation and recordings.

The dorsal and ventral roots were stimulated optically by Holmium: YAG laser (wavelength = 2.12 μm; pulse duration = 350 μs) and the compound nerve action potentials (CNAPs) were recorded from ipsilateral sciatic nerve just before branching. The stimulation threshold for observing the CNAPs from the sciatic nerve following optical stimulation of ventral and dorsal root potentials was about 0.8 J/cm2. Similarly the ipsilateral sciatic nerve was also stimulated both electrically and optically and the corresponding ventral and dorsal root potentials were recorded separately. Pulsed laser-light evoked action potentials (PLLEAPs) of sciatic nerve, dorsal and ventral roots were compared with electrically evoked action potentials (EEAPs) for the shape and latency. The shape and timing of PLLEAPs are similar to EEAPs indicates the conduction velocities are equal. However, the amplitude of PLLEAPs was much smaller compare to EEAPs, suggestive of the superior spatial selectivity of optical stimulation.

The above results suggest that it is possible to stimulate both peripheral and central nervous system by low level pulsed infrared laser light. This novel neural stimulation approach may be employed for spinal stimulation of paraplegics and quadriplegics, deep brain stimulation in Parkinson diseases and essential tremor, and fMRI studies due to its advantages over electrical stimulation, such as artifact-free, damage-free, spatial specific stimulation, and magnet compatibility.

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Boron-Doped Diamond Neurosensors and Neural Stimulating Electrodes

Heidi B. Martin 1, Songtao Xie 1, Cynthia A. Chestek 2, Jeffrey M. Halpern 1, Geoffrey Shafer 3, Christopher G. Wilson 3, and Hillel J. Chiel 2

1 Chemical Engineering Department, Case Western Reserve University, Cleveland, Ohio
2 Biology Department, Case Western Reserve University, Cleveland, Ohio
3 Pediatrics Department, Case Western Reserve University, Cleveland, Ohio

Conductive diamond provides unique opportunity to integrate sensing and stimulation in the same device. This presentation focuses on fabrication of functionalized diamond-film microelectrodes and application toward (a) *in vitro* detection of neurotransmitters and neuromodulators: dopamine, adenosine and serotonin, (b) detection of neural activity and (c) stimulation of neural activity.

Boron-doped diamond is a chemically and mechanically robust electrode that enables new chemistries and lower analyte concentrations to be investigated because of its extremely wide potential window of water stability and low baseline current, respectively. Diamond electrodes do not form a surface oxide and resist fouling, demonstrating the most stable response of any carbon-based electrode, also without requiring extensive pretreatment to regenerate the electroactive surface, all advantages for tissue implantation. Its surface chemistry inhibits oxygen reduction and provides advantage in chemical functionalization to enhance sensor specificity.

Diamond microneedle electrodes were fabricated using chemical vapor deposition to selectively deposit diamond onto a tungsten microelectrode. Electrochemical detection at millisecond time scales by fast scan cyclic voltammetry monitored chemical release. As-grown, hydrogen-terminated diamond detected 1 nM serotonin, 1 nM dopamine and 10 nm adenosine in flow cell calibration; oxygen terminated diamond was less sensitive, but maintained a stable response for extended time periods. Distinction between serotonin, dopamine, adenosine, ascorbic acid and DOPAC within mixtures was also possible.

Through real-time electrochemical detection, we are investigating adenosine's role in modulation of the mammalian respiratory neural network, utilizing rat-pup brainstem slices that exhibit fictive inspiratory drive. Initial studies showed that administration of a specific adenosine A_{2A} receptor agonist, CGS21680, induces adenosine release at concentrations high enough to activate A_{2A} receptors. Additionally, in recent experiments, we have seen inhibition of a compound with dopamine's electrochemical signature.

In working toward an integrated device, each capability is being tested individually *in vitro* in the nervous system of the marine mollusk, *Aplysia californica*. The electrically coupled B4/B5 neurons are being used to show specific, one-to-one, stimulation and recording extracellularly outside the insulative sheath. To monitor stimulated chemical release from specific cells, we first determined that the metacerebral cell (MCC), containing serotonin, has projections to the I2 muscle. Serotonin release at the I2 muscle by MCC stimulation was then qualitatively detected

at the diamond sensor. Presently, we are focusing on quantitative serotonin detection, and coupling chemical and electrical recording, as well as stimulation.

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Microlesions associated with depth electrode implantation

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

[1]*Department of Engineering Science and Mechanics, Pennsylvania State University, State College, Pennsylvania*
[2]*Department of Electrical and Computer Engineering, George Mason University, Fairfax, VA*
[3]*Children's National Medical Center, Washington, DC 20010, USA*
[4]*Department of Neurosurgery, Pennsylvania State University, State College, Pennsylvania*

Studies of deep brain stimulation (DBS) patients reveal functional effects independent of electrical stimulation. Electrodes implanted in the brain necessarily cause lesions in tissue irrespective of their use in electrical stimulation. We present a study of the anatomy of lesions caused by unilateral, transient and bilateral hippocampal depth electrode implantation in rats, as compared with sham implant controls. Stereological quantification of the following phenomena was performed: neurodegeneration (using both Amino Cupric Silver stain and Fluoro Jade B), GFAP expression and microglial activation (using both silver and OX42 stains).

All work was performed with IACUC approval. Male Sprague-Dawley rats (300g) were anesthetized and either underwent sham surgery or were implanted unilaterally or bilaterally with stainless steel electrodes (250 micron diameter) into the ventral hippocampus. A subset of unilateral implants were transient (i.e. electrode was removed before end of surgery). Animals were allowed to recover 2, 5, 10 or 21 days after surgery before sacrifice and perfusion. Brains were histologically prepared and stained and sections were investigated stereologically for number of activated microglia and area fraction of degeneration and GFAP expression.

Amino-cupric Silver stain revealed significant degeneration in areas distant from the site of electrode implantation, in some cases even in the contralateral hippocampus of unilaterally implanted animals. Patterns of degeneration were consistent with damage to axonal projections within the hippocampus. Gliosis and the presence of activated microglia are contained to an area proximal to the electrode track. Therefore the extent of the damage is not obvious in tissue stained for GFAP or activated microglia or with Nissl stain. For investigators wishing to determine the full range of damage due to implanted electrodes, a stain designed specifically for degenerating neurons is necessary. These results are relevant both to the designers of brain-machine interface technologies and clinicians using DBS.

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Polymer Coatings on Silicone Reduce Tissue Fouling

J. P. (Pat) McAllister II[1], Xuemei Liang[2], Haiying Tang[2], William Grever[3], Kruti Patel[1], Richard Keep[4], Jianming Xiang[4], Kelley Brabant[1], Carolyn A. Black[1], Anfeng Wang[2], Ting Cao[2], Steven O. Salley[2], Golam Newaz[5], Gregory W. Auner[6], and K. Y. Simon Ng[2]

[1] *Department of Neurological Surgery, Wayne State University School of Medicine, Detroit, MI*
[2] *Department of Chemical Engineering and Materials Science, Wayne State University, Detroit, MI*
[3] *Children's Research Center of Michigan, Department of Pediatrics, Wayne State University, School of Medicine, Detroit, MI*
[4] *Department of Neurosurgery, University of Michigan, Ann Arbor, MI*
[5] *Department of Mechanical Engineering, Wayne State University, Detroit, MI*
[6] *Department of Electrical and Computer Engineering and Smart Sensors and Integrated Microsystems (SSIM) Program, Wayne State University, Detroit, MI*

Silicone catheters have vastly improved medical treatments, especially for hydrocephalus, but functionality is often compromised by tissue obstruction. In this study, silicone surfaces coated with biopolymers (heparin, hyaluronan) and self-assembled monolayers (SAM) (octadecyltrichlorosilane-OTS, fluoroalkylsilane -FAS) were investigated to determine the effect of these coatings on astrocyte and choroid plexus cell growth. Chemical vapor deposition, plasma treatment and photo-immobilization methods were used for coating FAS, OTS, and heparin/hyaluronan onto silicone, respectively. Contact angle measurements determined the hydrophobicity and stability of the coatings. Enriched astrocyte and choroid plexus cells were cultured on silicone samples for one and two weeks, respectively, and cell counts were performed to measure growth. Acute and chronic in vivo tests were also conducted by surgically implanting coated silicone discs into the cisterna magna of adult rats. The hydrophobic/hydrophilic properties of the coatings remained stable for 30 days. Compared to unmodified silicone, astrocyte proliferation was significantly ($p<0.05$) reduced on FAS-coated surfaces, while no significant difference was observed on OTS. In contrast, heparin and hyaluronan coatings increased astrocyte ($p<0.001$) and choroid plexus cell ($p<0.05$) growth. No significant reduction in choroid plexus cell proliferation was observed on FAS- or OTS-coated surfaces. Low cell growth may be attributed to hydrophobicity of the surfaces. Atomic force microscopy measurements revealed that silicone had the roughest surface and coatings decreased the surface roughness, but this feature did not play an important role on cell growth. The results indicate that silicone catheters coated with FAS may resist tissue obstruction and thus improve long-term implantation.

EMG-Triggered Eye Blink Neuroprosthesis

Daniel McDonnall[1], M. Douglas Gossman[2], and K. Shane Guillory[1]

[1]*Ripple, LLC, Salt Lake City, UT*
[2]*Ophthalmology Department, University of Louisville, Louisville, KY*

Patients with facial nerve damage suffer substantial disfigurement and dysfunction due to the loss of ability to convey facial expression and produce eye blink. The loss of function of the orbicularis oculi muscle (OOM), which produces eye blink, also makes patients highly susceptible to related eye pain, eye infection, and, in many cases, loss of the affected eye. Given the lack of effective therapies, complications related to the loss of eye blink and vision are profoundly disturbing for these patients.

In this presentation, we discuss the creation of a totally implantable stimulator device that can restore eye blink in patients with unilateral facial nerve paralysis. The system will record EMG from the intact eye to detect normal blink and stimulate the muscle of the paralyzed eye to create a synchronous blink.

The ability to evoke eye blink via direct stimulation of dennervated OOM triggered by EMG signals from the contralateral intact eyelid has been demonstrated in canines. Further refinement of OOM stimulation was investigated in a study of the effectiveness of single-channel versus multiple-channel electrical stimulation to restore a complete and cosmetically acceptable eye blink. Bilateral OOM paralysis was performed in eight dogs; the OOM of one side was directly stimulated using single-channel electrical stimulation and the opposite side was stimulated using four channel electrical stimulation (two in the upper lid and two in the lower lid). Multi-channel stimulation exhibited significantly lower twitch stimulation thresholds than single-channel stimulation, and only multi-channel stimulation produced complete eyelid closure.

The number of animal studies demonstrating successful complete palpebral closure via exogenous stimulation of paralyzed OOMs strongly supports a proof-of-concept study for human subjects. In Phase I of this program, we will perform this study to confirm this effectiveness in human subjects and identify proper electrode placement and stimulation for functional and cosmetically acceptable eye closure.

Successful functional eye blink will require sufficient eye closure to keep the eye moist. This will be evaluated as the repeatable excitation of OOM to lower the upper eyelid to close the eyelid as recorded by a high-speed video camera. To improve cosmesis, the blink must match the kinetics of the contralateral normal blink. Therefore recorded blinks should have a timing of 30 to 150 ms for the closure phase and 100 to 300 ms for opening. Stimulation must be sufficient to produce complete eye closure, but it must not spillover to excite adjacent facial musculature.

This work is currently pending funding from a National Eye Institute SBIR grant.

Development of a Bi-Directional Brain Machine Interface

Lee E. Miller[1], Andrew H. Fagg[2], Nicholas G. Hatsopoulos[3], Ferdinando A. Mussa-Ivaldi[1], Sara A. Solla[1]

(1) Dept of Physiology, Northwestern University Medical School, Chicago, IL
(2) School of Computer Science, University of Oklahoma, Norman, OK
(3) Dept of Organismal Biology and Anatomy, University of Chicago, Chicago, IL

It is now possible to use recordings from motor areas of the brain to control a computer display or a robotic limb. Most of these motor-related BMIs act as position controllers, and ignore the dynamics of the musculoskeletal system. Furthermore, feedback in these BMIs has been supplied entirely by the visual system. Our work attempts to address these limitations by developing a *bidirectional* interface that produces movement of a more complex, but natural dynamical limb, and provides feedback about the movement by direct, electrical stimulation of the brain.

Monkey subjects were trained to execute a 2-dimensional tracking task. 100-electrode recordings from M1 comprise a high-dimensional control signal that must be mapped onto these 2 dimensions. Recently, we discovered that the unsupervised, nonlinear Isomap algorithm can preserve 2-3 times more information about the mapping from neural space to physical space than do linear methods like PCA. We have also compared the predictions of Cartesian hand position to that of joint torque. Torque prediction was comparable, and in some cases, better than position, despite the fact that the torque signals had higher frequency content. Torque predictions that included delayed limb state (simulating proprioceptive feedback) were significantly better than those based cell activity alone. We intend to compare closed-loop "brain control" based on kinetic predictions to that achieved using kinematic predictions.

We have also begun to test different methods to supply non-visual feedback. In one approach, monkey subjects were trained to control a cursor using position predictions derived from recorded M1 signals. This standard closed-loop brain control was compared to conditions in which predictions were used to control a powered exoskeleton along with the cursor. The monkey's arm was fastened to the exoskeleton, such that it served as a proprioceptive feedback channel. Under certain conditions, control of the cursor (assessed by the time to reach targets) improved more readily over time with this additional feedback.

While these results may provide important information about the role of proprioception, this approach would not be helpful to a spinal injured patient without intact spinal afferent input. Consequently, we are also testing artificial proprioception achieved by electrically stimulating the primary somatosensory cortex. We have shown that it is possible for a monkey to discriminate different stimulus frequencies, and hope to extend this work to convey limb state information using time varying stimulus trains.

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EMG Prediction and the Development of a Primate Model of Cortically Controlled FES for Grasp

Lee E. Miller[1], Eric J. Perreault[2], Eric A. Pohlmeyer[1], Marc W. Slutzky[3], Kevin L. Kilgore[4], Robert F. Kirsch[4], Dawn Taylor[4]

(1) Dept of Physiology, Northwestern University Medical School, Chicago, IL
(2) Dept of Neurology, Northwestern University Medical School, Chicago, IL
(3) Dept of Biomedical Engineering, Northwestern University, Evanston, IL
(4) Dept of Biomedical Engineering, Case Western Reserve University, Cleveland, OH

In the past several years, our group at Northwestern University has successfully predicted limb muscle activity from multi-electrode recordings in primary motor cortex (M1). Recently, together with colleagues at Case Western University, we have begun to develop a primate model to test the feasibility of using recordings from M1 together with functional electrical stimulation (FES) to restore grasp to paralyzed patients. FES has great potential in a variety of applications, but independently controlling the many degrees of freedom of hand movements is not yet possible. In the Freehand clinical FES system, control of grasp is along a single degree of freedom, with muscles stimulated in preprogrammed combinations to form one of several stereotypic grasps. Cortical recordings might offer more dexterous and natural control.

We have comparable muscle prediction results from two monkeys. Useful recordings continue from the second monkey, now over 18 months after the original implant. Predictions made using multiple input linear filters account for as much as 60-75% of the variance of EMG during reaching and grasping movements. Non-linear models can increase VAF by 5-10 %. In some cases, prediction quality has persisted for 1-2 weeks before it was necessary to recalculate the filters. Our goal is to use predictions like these as FES control signals. We are currently developing stimulus methods using percutaneous, intramuscular electrodes. Ultimately we anticipate using either chronically implanted intramuscular or nerve electrodes.

A key component of this model is the need to induce a transient paralysis of the monkey's limb. We have tested a variety of local anesthetics to determine their efficacy to induce grasp deficits by blocking the median and ulnar nerves. Achieving a nerve block by normal methods in an awake monkey is virtually impossible. Therefore, we have developed a method using nerve cuffs connected to subdermal injection ports. We can achieve near complete blocks of the wrist and digit flexors of 2-5 hour duration with simple injections into these ports.

Together the EMG predictions, nerve block, and muscle stimulation provide the means to investigate whether muscle activity predictions based on cortical recordings can be used to activate those muscles in real-time and allow a monkey with a paralyzed arm to form a functional grasp.

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Activation of fiber tracts surrounding the subthalamic nucleus during deep brain stimulation: model predictions and experimental results

Svjetlana Miocinovic[1,2], Scott F. Lempka[1,2], Weidong Xu[3], Gary S. Russo[3], Jerrold L. Vitek[3], Cameron C. McIntyre[1,2]
[1]*Dept of Biomedical Engineering, Cleveland Clinic, Cleveland, Ohio*
[2]*Dept of Biomedical Engineering, Case Western Reserve University, Cleveland, Ohio*
[3]*Dept of Neurosciences, Cleveland Clinic, Cleveland, Ohio*

The subthalamic nucleus (STN) is the most common target for deep brain stimulation (DBS) treatment for Parkinson's disease. However, STN DBS electrodes are placed in close proximity to several fiber tracts that can be activated during stimulation. The activation of corticospinal tract (CST) fibers passing through the internal capsule causes unwanted muscle contractions. On the other hand, the activation of pallidothalamic fibers passing through the lenticular fasciculus (LF) could potentially be a therapeutic target of the stimulation. Predicting activation of these fibers tracts on a subject-by-subject basis could help anticipate and avoid side effects, as well as enable definition of stimulation parameter settings that may improve therapeutic outcomes.

We created anatomically and biophysically realistic computer models of the STN and surrounding fibers tracts for three macaques implanted with scaled DBS systems. The models contained 50 CST and 50 LF fibers to which we applied extracellular voltage produced by the DBS electrode. We calculated the percentage of fibers that were activated for a given set of stimulation parameters. In two animals we used microelectrode recording data from the internal globus pallidus (GPi) as a measure of antidromic LF activation. Visually observed muscle contractions and electromyography (EMG) recordings were used to evaluate CST activation.

In monkey Y 41% of GPi cells fired at short latency (< 1.5 ms) following therapeutic DBS parameter settings and 8% of GPi cells fired within the same time period in monkey S. The model predicted that 82% and 18% of LF fibers were activated for the same stimulation parameters, matching our experimental results because only about half of GPi fibers pass through LF. In the same two monkeys CST activation thresholds were 3V and 3.5V which in the model produced CST activation of 11% and 9%. In monkey M experimentally measured CST thresholds for monopolar stimulation were 1.1, 1.1, 1.3 and 1.6V for the four electrode contacts. The comparable model predictions were 1.0, 1.4, 1.4 and 1.5V for 5% CST activation.

Our STN DBS model customized to each animal's anatomy and electrode position produces accurate predictions of CST and LF fiber activation. In addition, our modeling concepts can be used to design experiments and select stimulation parameter settings to achieve specific activation of targeted fiber tracts.

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Single-Chip Wireless Microsystems for Multichannel Neural Biopotential Recording

Pedram Mohseni[1] *and Khalil Najafi*[2]

[1]*Departmet of Electrical Engineering and Computer Science, Case Western Reserve University, Cleveland, OH*
[2]*Department of Electrical Engineering and Computer Science, University of Michigan, Ann Arbor, MI*

Topic area: Neural Interfaces & Microsystems

We have developed single-chip low-power wireless microsystems, fabricated using a 1.5-µm double-poly double-metal n-well standard CMOS process, that can be used with micromachined recording microelectrode arrays for interfacing with the central nervous system at the cellular level in unrestrained biological hosts.

In particular, two wireless battery-powered recording microsystems for multichannel neural interfacing have been developed that combine ac amplification, dc baseline stabilization, clock generation, time-division multiplexing, and wireless FM transmission of µV- and mV-range input biopotentials on chips interfaced with only three off-chip components. The 4-channel recording device measures $1.7 \times 1.2 \times 0.16\text{cm}^3$ and weighs 1.1g including two miniature batteries whereas the 8-channel recording system measures $2.1 \times 2.1 \times 0.16\text{cm}^3$ and weighs 2.2g. They dissipate <2.2mW from a 3-V power supply, which is the lowest total power consumption yet reported. The systems electrical characteristics have been fully characterized via benchtop and *in vitro* tests in saline using two different neural recording microelectrodes. Successful single-channel wireless *in vivo* recordings of neural activity in the auditory cortex of an awake marmoset monkey have been performed at 96.2MHz at several transmission ranges up to 0.5m with measured SNR >8.4dB.

Finally, a telemetry command receiver integrated with a multichannel neural recording transmitter is developed for wireless site selection and site monitoring within a $4.6 \times 4.6\text{-mm}^2$ bi-directional biotelemetry chip. The receiver is designed to select seven recording sites from a total of 28 available sites according to four pre-defined site selection patterns and to perform power management via a 1-MHz Manchester-encoded ASK link. Detailed system simulation results together with preliminary measurement results from a fabricated prototype receiver are presented.

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Classification and Prediction of EEG Signals Preceding Four Movements, Real and Imagined

Valerie Morash 1,2, Ou Bai 2, Stephen Furlani 2, Mark Hallett 2
1 Department of Brain and Cognitive Sciences, Department of Electrical Engineering and Computer Science, Massachusetts Institute of Technology, Cambridge, MA
2 National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD

Patients that suffer from loss of motor control would benefit from a brain-computer interface (BCI) that would, optimally, be noninvasive, allow multiple dimensions of control, and be controlled with quick and simple means. Ideally, the control mechanism would be natural to the patient so that little training would be required; and the device would respond to these control signals in a predictable way and on a predictable time scale. It would also be important for such a device to be usable by patients capable and incapable of making physical movements.

A BCI was created that used electroencephalography (EEG). Multiple dimensions of control were achieved through the movement or motor imagery of the right hand, left hand, tongue, and right foot. The movements were non-sustained to be convenient for the user. The BCI used the 1.5 seconds of the Bereitschaftspotential prior to movement or motor imagery for classification. This could allow the BCI to execute an action on a time scale anticipated by the user.

To test this BCI, eight healthy participants were fitted with 29 EEG electrodes over their sensorimotor cortex and one bipolar electrooculography electrode to detect eye movement. Each participant completed six blocks of 100 trials. A trial included visual presentation of three stimuli: a cross, an arrow, and a diamond. Participants rested during the presentation of the cross. The arrow indicated the action that the participant should perform: right hand squeeze, left hand squeeze, press of the tongue against the roof of the mouth, or right foot toe curl. The diamond indicated that the participant should execute the movement during the first three blocks; and that the participant should imagine executing the movement during the last three blocks.

Trials affected by motion artifacts, in particular face muscle activity, were removed. Of the remaining data, about 80% were used to train a Bayesian classification and about 20% were used to test this classification. Prediction of the four movements reached accuracies above 150% that of random classification for both real and imagined movements. This suggests a promising future for this BCI.

This research was supported by the Intramural Research Program of the NIH, National Institute of Neurological Disorders and Stroke.

VLSI for Multimodal Neuro-Monitoring

K. Murari[1], M. Mollazadeh[1], C. Sauer[1], M. Stanacevic[2], G. Cauwenberghs[3], N. Thakor[1]

[1]Dept. of Biomedical Engg., Johns Hopkins University, Baltimore, MD.
[2]Dept. of Electrical and Computer Engg., State University of New York, Stony Brook, NY.
[3]Dept. of Neurobiology, University of California San Diego, La Jolla, CA.

Long term, real-time monitoring of brain activity is of tremendous use in understanding neurological events and disorders. The coupling between neurochemical and electrical activity in the central nervous system (CNS) makes the simultaneous detection and monitoring of neurochemical and electrophysiological field potentials very attractive. Very Large Scale Integrated (VLSI) circuits offer the potential of low power devices with a very small footprint that can perform such monitoring. Here, we present discrete VLSI systems for multimodal neurological sensing with a wireless power-up and telemetry interface. The first system is a 16 channel VLSI potentiostat with picoampere sensitivity for detecting neurotransmitter activities. The potentiostat consumes 12.5 μA per channel and has a digitally programmable gain that allows it to measure neurotransmitter concentrations from nanomolar to millimolar. The second is a 15 channel EEG recording system that is designed to sample field potential data at up to 2 kHz. The tunable bandpass filters in the circuit allow the recording of either field potentials (1 - 200 Hz) or neural spike signals (1 Hz - 8 kHz). Both systems incorporate a configurable analog-to-digital converter (ADC) to convert the neurochemical or electrophysiological signals into serial bit-streams. The third system is a power harvesting and telemetry module receiving power and clocks wirelessly over an inductively coupled link. The system uses the same link to telemeter the recorded data out of the potentiostat and/or the EEG recording chip. The module harvests power and generates two regulated 3.3 V supplies and clocks to run the systems. Up to 2.2 mA of current can be drawn from the harvesting module over a range of 3 cm. We demonstrate wireless powering and transmission of recorded electrical and real-time dopamine data. We plan to integrate all the systems into a single silicon die that would be released as a standalone implantable probe.

This work was supported by NIH MH062444 065296, DARPA and the Whitaker Foundation. Chips were fabricated through the MOSIS foundry service.

TOPIC AREA: OTHER/NEURAL MICROSYSTEMS.

Locations of the Active Contacts with Respect to the STN in Patients with Ideal Clinical Outcomes Following DBS Implantation for Parkinson's Disease

Richard Murrow 1; Danielle Englert 1; Eldad Hadar 2
1 Department of Neurology, University of North Carolina, Chapel Hill, NC
2 Department of Neurosurgery, University of North Carolina, Chapel Hill, NC

Deep brain stimulation (DBS) therapy of the subthalamic nucleus (STN) for Parkinson's disease (PD) can produce striking clinical outcomes. When outcomes are not ideal, the electrode is often believed to be misplaced. The precise target within or near the subthalamic nucleus (STN) for optimal clinical outcomes in PD patients, however, has not been universally agreed upon. In an effort to better define this target, we report the positions of the active contacts in patients who had ideal clinical outcomes following DBS surgery for PD. This position is given in relationship to the individual's STN, in addition to the patient's anterior commissure – posterior commissure (AC-PC) line, because it is the STN which is felt to contain the most relevant neural circuits.

Between April 2004 and June 2006, 35 patients were surgically treated for PD with implantation of DBS electrodes in the STN and had their generators implanted and programmed. Of these patients, 27 (77%) had ideal clinical outcomes, which we defined as patients who post-operatively required 200 mg of levo-dopa or less and whose post-operative on-stimulation UPDRS scores were equivalent to or better than their pre-operative on-medication UPDRS scores. Pre-operative isotropic T1 and proton-density MRI images, and post-operative T1 MRI images were obtained for all of the patients. Targeting was based upon direct visualization of the superior, lateral, and posterior STN on the proton-density sequences. Post-operative images were merged with preoperative images using Medtronic Stealthstation Framelink software. The positions of the active contacts were then compared with the locations of that patient's STN as identified on the pre-operative imaging.

The active contacts were found to be within the superior, lateral, and posterior portion of the STN, the region believed by many to correspond to the sensorimotor sub-region of the STN. On the axial images the active contacts were 1-3 mm below the AC-PC plane. The locations of the active contacts of the 8 patients who did not achieve superior results were also examined – these patients had lead placements that were less precise.

These results suggest that direct targeting of the sensorimotor portion of the STN, when successful, results in ideal patient outcomes. Our results suggest that clinical success with deep brain stimulation in PD depends upon the ability to deliver the active contact to the sensorimotor STN and that technologies and techniques which improve this capability will improve DBS efficacy with PD.

Topic: Deep Brain Stimulation

Developing An Artificial Neural Network Controller For Automated Standing Balance Using Functional Neuromuscular Stimulation (fns) Following Spinal Cord Injury (sci)

Raviraj Nataraj[1], Musa L. Audu Ph.D.[1,2], Robert F. Kirsch Ph.D.[1,2], Ronald J. Triolo Ph.D.[1,2]

1) Dept. of Biomedical Engineering, Case Western Reserve University
2) Cleveland VA Medical Center

This project uses a model-based approach to develop a controller for standing balance by functional electrical stimulation (FES) following spinal cord injury (SCI). Current FES standing systems implement open-loop stimulation to extend and stiffen lower-extremity joints for standing maintenance. The user must then rely on an assistive device (ex: walker) in response to balance disturbances. We seek to implement sensor-based controller feedback to assess disturbances and modulate muscle stimulations to automatically assist in standing balance.

Our approach is to verify a desirable controller scheme in simulation prior to physical implementation to minimize on-line testing with live subjects. We use a computational bipedal model of human stance to determine optimal muscle excitation patterns and run controller simulations. The three-dimensional model consists of 15 degrees of freedom (DOFs), passive joint properties, and 52 Hill-type muscles. To ensure successful clinical implementation, the final system must comply with standards of minimal instrumentation, efficient operation, and controller effectiveness. To this end, we implement artificial neural networks (ANNs) at various stages for system identification, predictive modeling, and pattern learning of non-linear systems. To date, we have verified ANN-prediction of center of pressure (COP) in able-bodied individuals for learning and actuating pro-active kinematic responses to perturbation. In addition, an ANN actuator has been trained on optimized muscle excitation data across a feasible, static posture space to achieve successful perturbation rejection on an ankle-modulated system in simulation under proportional-integral-derivative (PID) control. Finally, an ANN using pelvic position inputs accurately identifies lower-extremity joint angles that can then be used for state-feedback control.

Future development includes ANN actuator training on optimal standing trajectories to attain desired synergistic actuation across all DOFs. The addition of fuzzy predictive control to baseline ANN actuation should augment performance by compensating for the inherent delay in peak muscle force-actuation following initial stimulation.

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Bioencapsulation of Neural Devices Using Laser Microjoining

Golam M. Newaz[1], Daniel Georgiev[2], James P. McAllister II[3], Taslema Sultana[4]
Simon Ng[4], Gregory W. Auner[5], and Hans Herfurth[6]

[1]Department of Mechanical Engineering, Wayne State University, Detroit, MI
[2]Department of Electrical and Computer Engineering, Wayne State University, Detroit, MI
[3]Department of Neurological Surgery, Wayne State University, Detroit, MI
[4]Department of Chemical Engineering, Wayne State University, Detroit, MI
[5]Department of Electrical and Computer Engineering, Wayne State University, Detroit, MI
[6]Center for Laser Technology, Fraunhofer USA, Plymouth, MI 48170

Laser microjoining offers unparalleled design flexibility in miniaturization of biomedical devices made with a wide variety of dissimilar materials. In a large number of specific applications, laser joining technologies can or have the potential to successfully compete with conventional joining technologies such as anodic bonding, eutectic bonding, soldering, brazing, gluing, and ultrasonic welding. The unique capabilities of laser processing offer opportunities to solve some of the fundamental issues of joining critical materials in miniaturized neural devices. The laser beam can be focused to a spot diameter of several tens of micrometers and can be easily controlled to deposit the exact amount of energy needed to join two parts. The result is minimal distortion or change of material properties in the part. In addition, the consistent quality and repeatability of laser processing enable reliable, hermetic sealing. Assessment of neural biocompatibility requires that materials be tested with exposure in neural fluids. Laser bonded microjoint samples made from Ti coated glass substrate and polyimide film (GPI) and titanium foil and polyimide film (TIPI) were evaluated for mechanical performance before and after exposure in artificial cerebrospinal fluid (CSF) for two, four, and 12 weeks at 37°C. These samples represent a critical feature, i.e., the microjoint—a major weakness in the bioencapsulation system. Both material systems showed initial degradation up to 4 weeks which then stabilized afterwards and retained similar strength until 12 weeks. The TIPI system appears to exhibit better overall performance with less degradation compared to its as-received strength. The CSF exposed TIPI samples predominantly failed at the interface, while GPI samples had mixed glass and polyimide substrate and interface failure. The amount of glass failure decreases and interface failure increases with increase in CSF exposure time. The failure mechanism of the as-received (not exposed to CSF) GPI samples under lap-shear was predominantly flexure type failure of the glass substrate. Hermetic sealing properties of the two material systems also show good promise. The in-vivo experiments provide promising data to conduct extensive in-vitro evaluation of laser bonds for bioencapsulation of neural devices.

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Vertically-Aligned Carbon Nanofiber (VACNF) Array for 3D Neural Electrical Interface

T.D. Barbara Nguyen-Vu, Hua Chen, Alan Cassell, M. Meyyappan, Russell Andrews, and Jun Li*

Center for Nanotechnology, NASA Ames Research Center, Moffett Field, CA 94035

Abstract

Developing biomaterial constructs that closely mimic the natural tissue microenvironment with its complex chemical and physical cues is essential for improving the function and reliability of implantable devices, especially neural-electrical interfaces. Here we demonstrate that free-standing (VACNF) arrays can be used as a multifunctional 3D brush-like matrix that interpenetrates the neuronal network of PC12 cells. Additionally, we report of that micro-patterned VACNF arrays are individually addressed and can be selectively electrically controlled for tailored modification and refined spatial-temporal resolution in neural devices.

VACNFs are grown from pre-fabricated microcircuits using plasma enhanced chemical vapor deposition (PECVD) and standard semiconductor processes, enabling them to be directly integrated in electronic devices. Such fabrication method creates a structure that enhances 3D interaction with surround tissue as compared to traditional 2D neural-electrical interfaces. Due to its 3D nanostructure and large effective surface area, VACNF arrays possess desirable electrical properties, such as large capacitance, for less harmful neural stimulation.

In addition to exhibiting excellent electrical properties, the CNF arrays provide a versatile template for modification with electronic-conducting polymers such as polypyrrole (PPy) to further improve the interface. First, the PPy enhances the electrical quality of the

surface by adding an element of pseudo-capacitance. Secondly, a thin conformal coating of PPy helps to increase the mechanical strength of the CNFs to provide an assembly of free-standing CNFs that are soft and flexible yet resilient enough to withstanding multiple wetting and drying cycles. The combined structure helps to maintain the integrity of both the CNFs and polymer film in the challenging aqueous environment of biological systems. We have also shown that the PPy film can be tuned with various anionic dopants to promote or prevent adhesion of PC12 cells, a model neuronal cell type derived from the rat pheochromocytoma. The cells normal morphology when grown on the CNF arrays establishing suitable biocompatibility of the material. Examination of cytotoxicity revealed no acute toxicity from either the CNF or the PPy films. We found that PC12 cells cultured with nerve growth factor (NGF) on VACNF substrates can form extended neural network upon proper chemical and biochemical modifications of the substrate.

The soft 3D VACNF architecture provides a new platform to fine-tune the topographical, mechanical, chemical, and electrical cues at sub-cellular nanoscale. Micropatterned multiplex VACNF arrays can be selectively controlled by electrical and electrochemical methods to provide localized stimulation with extraordinary spatiotemporal resolution. Further development of this technology may potentially result in a highly multiplex close-loop system with multi-functionalities for neuromodulation and neuroprostheses.

Development of a Brain Implantable Microsystem with Infrared Optical Telemetry for Advanced Neuromotor Prosthesis

A. V. Nurmikko[1], Y.-K. Song[1], W. R. Patterson[1], C. W. Bull[1], M. D. Serruya[1], M. R. Fellows[2], J. D. Simeral[2], and J. P. Donoghue[2]

[1]Division of Engineering, Brown University, Providence RI 02912, USA
[2]Department of Neuroscience, Brown University, Providence RI 02912, USA

Cortical control provides potentially the most natural and extensive command control source for severely disabled individuals. Ideally, a future cortical brain interface neural prosthetic system would be implantable, enabling a patient wearable system via transcutanoeus telemetry from the implant.

We have developed a prototype cortical neural interface system for brain implantable neuroprosthesis. The system is designed for neural recording from primates by converting cortical signals to a wireless digital stream of infrared light pulses as the output. The ultralow power implantable unit employs flexible liquid crystal polymer (LCP) substrate for integration of analog/digital microelectronic and optoelectronic chips, while adapting to geometrical constraints of the physiological and anatomical environment of the brain and adjacent subcutaneous space.

Our microsystem is composed of two electrically interconnected islands on the LCP substrate, with a front panel directly implanted to the cortex and a back panel which resides between the skull and the skin in a non-human or human primate. The overall microsystem design has a form factor based on input from neurosurgeons, neurologists, as well as a number of microdevice and engineering constraints. The front panel houses the cortical microelectrode array, fully integrated to an ultra-low power analog CMOS chip. The custom designed and fabricated CMOS IC includes preamplifier and multiplexing circuitry, and a unique hybrid flip-chip bonding technique was developed to fabricate a functional, encapsulated microminiaturized cortical device. The multiplexed analog signals are routed onto the peripheral circuits of the “back end” panel of the implant onto which additional components are integrated, including a low-power A/D converter, digital control-and-command chip, a microcrystal photovoltaic energy converter, and a low threshold current semiconductor laser for transcutaneous/transdermal infrared data link. Extraction of the digitized neural signals from the neural interface unit is performed either via a free space beam from the laser (at 850 nm in the skin transparent wavelength regime) or via a fiber optic coupled on-chip optoelectronic data interface to a thoracic unit in the chest. The power delivery to the microelectronic components takes place either via a microcrystal photovoltaic energy converter of input infrared power, or via an inductively coupled RF link, depending on application details. A 16-channel version of the system has been tested in in-vivo experiments measuring neural activity from the somatosensory cortex of rats, and diagnostic performance testing in monkeys is under way.

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Initiated Chemical Vapor Deposition of Biopassivation Coatings

W. S. O'Shaughnessy[1], D.J. Edell[2], and K. K. Gleason[1]

1 Department of Chemical Engineering, Massachusetts Institute of Technology
2 Innersea Technology Inc., Bethesda 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 microns in order to provide the required electrical insulation. This requirement significantly increases the diameter of the neural probe shanks (often only 25-100 microns 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). Trivinyl-Trimethyl-Cyclotrisiloxane is utilized as a self crosslinking monomer, initiated by radical fragments generated from the thermal breakdown of Tert-Butyl Peroxide. Due to the three vinyl moieties present on the monomer, the resulting coating is a highly crosslinked organosilicon polymer matrix which is synthesized directly on the surface of the substrate. Deposition rates on the order of 25nm/min have been observed for this process. This novel material possesses a resistivity on the order of 5×10^{15} Ohm-cm, allowing for a coating thickness on the order of only 5 microns to provide the required electrical protection. 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 2 years. In addition, compatibility with neural cells has also been evaluated.

Material samples are prepared in a custom built vacuum reactor. Monomer and initiator species are fed as gases to the reactor where the initiator is then broken down by a resistively heated filament at a temperature of between 300°C and 500°C. In addition, the substrate temperature is independently controlled between 50°C and 80°C, allowing deposition on very heat sensitive substrates. This approach to thin film formulation allows greater control of film chemistry than traditional plasma or thermal CVD as the reaction pathways available for the monomer are severely limited by the benign reaction conditions at the surface. Common problems of liquid phase coating techniques such as non-uniform wetting of the substrate and entrainment of solvent are also avoided. Additionally, this methodology allows for easy copolymerization and the deposition of coatings of graded composition, due to the use of vinyl moieties for monomer reaction. As a result, this approach gives maximum flexibility for optimization of both bulk and surface material properties.

Compressed Sensing of Large-Scale Cortical Neural Activity

S. Chrispell 1 and Karim Oweiss 1

1 Electrical and Computer Eng. Department, Michigan State University, East Lansing, MI

Sensing ensemble neural activity at the cell and/or population levels is the first step towards designing a successful cortical implant. Extracting information from the sensed activity, however, is a nontrivial task, largely due to nonstationarity of the neuronal discharge patterns. In addition, when the implant is resource-constrained, a nontrivial optimization among power consumption, energy dissipation, communication bandwidth and sustained real-time operation in living brain tissue needs to be performed. Nevertheless, information can be efficiently extracted if *smart* signal processing is performed early in the data stream within the resource-constrained environment of an implanted chip.

Our previous work has shown that spatial and temporal processing of the multichannel neural data is feasible to optimize real-time data transfer within the limited telemetry bandwidth. Through a spatial whitening filter and a wavelet transform-based data compression scheme, the transmitted "principal" channels were shown to fully preserve both the temporal and rate information believed to encode the stimulus information in the spike trains. In this work, we propose two methods for *compressed sensing* of firing rate functions of neuronal ensembles. The first method builds on our previous work on performing spike sorting in the compression domain. This yields a sensing mechanism without resorting to data decompression off-chip. The second method relies on sensing rate functions without spike sorting, thereby directly interfacing the implant to the decoding and control components of a brain machine interface system.

We compare the proposed method to classical time-domain, spike sorting-based rate function extraction algorithms and show that decoding can be efficiently performed with the principal data channels in the compression domain. This feature enables substantial savings in computational expenses, chip size, and real-time functionality of a brain machine interface system. Moreover, it mitigates the need for hardware-friendly spike sorting algorithms, a highly controversial issue in the neuroscience community. We illustrate the performance using synthetic neural data mimicking intracortical recordings during an arm reach movement.

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Identification and tracking of spatial and temporal connectivity of large scale neuronal ensembles from multielectrode recorded mixtures

Karim Oweiss 1, Rong Jin 2, Feilong Chen 2, Yasir Suhail 3

1. Electrical and Computer Engineering Dept., Michigan State University, MI
2. Computer Science and Engineering Dept., Michigan State University, MI
3. Biomedical Engineering Dept., The Johns Hopkins University, MD

The dynamic identification of clusters of neurons with correlated spiking activity from large recorded ensembles is a nontrivial problem. Existing techniques quickly erode in the face of the high dimensionality, or when nonstationarity in neural firing is encountered due to brain plasticity. We propose a nonparametric analysis method to identify clusters of functionally interdependent neuronal populations, independent of the time scale at which they are maximally correlated and their relative location. The spike train of every neuron is represented in a *scale space*, where each neuron is a point object and connects to other neurons with a vertex that depends on a similarity measure. The similarity measure consists of an arbitrary defined statistic between any given pair of neurons. When Pearson correlation is used, the resulting measure expresses the correlation of the firing rates between the two neurons. On the other hand, when mutual information is used, the resulting measure expresses the information that both neurons may be receiving from a common input. A graph partitioning technique relying on spectral clustering is used to identify "similar" neurons by simultaneously maximizing the within-cluster similarity as well as minimizing the between-cluster similarity measures.

We simulated a population of 120 neurons in 4 different clusters of functionally interdependent neurons with 30 neurons each. In each cluster, a distinct pre-built neuronal model was synthesized. For each model, a set of parameters was set to determine its behavior. The parameters included firing threshold, resting potential and post-synaptic potential, noise mean, and noise standard deviation. The signaling parameters for cluster 1 and 2 were set to be similar, so are those for cluster 3 and 4, such that the two pairs will behave similarly. The noise parameters were varied among clusters to synthesize a variety of within-cluster distributions so as to induce more *stochastic* behavior in the neuronal firing. Neuronal spatial distribution was simulated using different designs of the recording electrode array and different patterns of synaptic connectivity.

Preliminary results indicate that the proposed technique is superior to existing spike train analysis techniques in identifying functionally interconnected neurons. Moreover, it allows mapping to single cluster neurons in "local" circuits that may possess time-locked or phase-locked temporal synchrony, as well as neurons in "global" circuits that exhibit slower temporal dependency arising later in the response. Capturing the causal dynamics of neuronal firing across multiple time scales is an essential feature that will allow the algorithm to track neuronal circuits as they are reconfigured during behavior and learning.

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Collagenase-Aided Insertion of Intracortical Microelectrode Arrays: Evaluation of Insertion Force and Chronic Recording Performance

Kunal J. Paralikar, Jonathan K. Lawrence, and Ryan S. Clement
Department of Bioengineering, The Pennsylvania State University, University Park, PA

Typically electrodes are required to puncture the intact pia mater during insertion which in the process can lead to brain dimpling and trauma. Furthermore, there is interest in the development of more flexible substrates to reduce relative micromotion after implantation, but such devices have difficulty penetrating the pia without buckling. In this paper a strategy for reducing the mechanical integrity of the pia's collagen network by treatment with collagenase is evaluated experimentally. Measurements of the insertion force were carried out with a load cell during slow (10μm/sec) electrode insertion into the cortex of rats. It is shown that controlled application of collagenase reduces the peak insertion force experienced by the microwire arrays around 30% on average. In addition, chronic neural recordings (up to 1 month) suggest that there is no appreciable difference in the signal quality as recorded from the collagenase treated and the control sites. Histology studies of the implanted sites are being pursued to evaluate any differences at the tissue-electrode interface between the collagenase treated and control sites. The results obtained thus far suggest the technique is useful for reducing insertion forces without compromising neural recording capabilities.

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Topic Area: Electrodes

Reversible Biofouling in Acutely Implanted Electrodeposited Iridium Oxide Film Electrodes

Nathalia Peixoto1, Nick Chernyy2, Ruchi Parekh2, Jonathan Mason2, Sridhar Sunderam2, Steven J. Schiff3,2, Bruce J. Gluckman2,3

1.Krasnow Institute for Advanced Study and Electrical and Computer Engineering, George Mason University, Fairfax, VA 22030
2.Engineering Science and Mechanics, and 3. Neurosurgery Department, Penn State University, University Park, PA 16802

Low-frequency (<<100 Hz), 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 are required, where current is primarily limited by electrochemistry at the electrode surfaces. Here we evaluate performance of electrodeposited iridium oxide film electrodes in acutely implanted animals.

Iridium oxide film was electrochemically deposited on stainless steel (3mm long x 0.25mm diameter) wire. Electrodes were characterized with cyclic voltammetry before and after film deposition, against a Ag/AgCl reference electrode, at 50mV/s, and immersed in phosphate buffered saline (pH 7.4). Charge storage capacity (CSC), defined as the charge delivered for one period of the cyclic voltammetry sweep, typically increases from 20μC to above 1000μC.

All procedures were carried out under GMU IACUC approval. Male Sprague-Dawley rats (300g) were anesthetized and bilaterally implanted, under stereotaxic guidance, with hippocampal electrodes. A Ag/AgCl pellet was positioned touching the skull and used as reference electrode. CSC was measured *in vivo* for each implanted electrode, using cyclic voltammetry (CV) with the same protocol as above. The charge delivered by implanted electrodes decreases to 65.5% (n=8) of the *in vitro* CSC. The CV spectrum of implanted electrodes changes substantially; no oxidation or reduction peaks are present.

Electrodes are explanted after the surgery, cleaned in ethanol, dried, and subsequently characterized in phosphate buffered saline. Iridium oxidation and reduction peaks are recovered in the post-implantation profiles, and the CSC is recovered to 90% of the original (pre-implantation) values.

These results point to the acute action of biofouling in implanted electrodes. Recovery of CSC demonstrates the mechanical stability of the deposited iridium oxide film. Despite the fact that lower charge is delivered to the tissue, the film does not delaminate or otherwise lose its charge capacity.

The biofouling on implanted electrodes limits the amount of current that can be 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 and recording electrodes.

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Proof of Concept for an LGN based Visual Prosthesis

John S. Pezaris and R. Clay Reid
Neurobiology Department, Harvard Medical School, Boston, MA 02115

The field of visual prosthetics has concentrated primarily on two targets for stimulation, the retina and the primary visual cortex. The lateral geniculate nucleus of the thalamus, the relay station between these two areas, has been ignored because of the difficult surgical approach. The development of deep brain stimulation techniques for addressing pathologies of the mid-brain has opened surgical access to the thalamus, and motivates a reconsideration of targets for visual prostheses.

Accordingly, we have performed a series of experiments in an animal model to demonstrate a proof of concept for a visual prosthesis based on thalamic microstimulation. To assess the characteristics of electrically-evoked percepts, we performed a study of electrical stimulation of LGN through fine wire electrodes in awake macaques, using behavioral reports to determine (1) percept location and (2) size and color.

(1) To demonstrate basic efficacy and to determine percept location, we used a center-out visually guided saccade paradigm where animals were required to foveate a central point and then saccade to briefly presented target stimuli. While most targets (and all fixation points) were presented on a computer screen, some targets were presented via electrical stimulation applied to fine wire electrodes placed in the LGN. Trials where the target appeared on the screen were used as a control baseline to compare against trials where the target was presented electrically.

Data were collected from two macaques. Each animal immediately generalized to the electrical targets, consistently saccading to a point in space which corresponded to the location of the previously mapped receptive field of cells at the electrode tip. Saccade latencies and accuracies to electrical targets were consistent with those to screen targets, suggestive of a perceptual rather than motor effect. This was verified through a small number of double-saccade experiments.

(2) To assess electrical percept size and color characteristics, we trained a match-to-sample task as follows. After fixation, a cue was briefly presented, and followed by a set of targets presented on the screen. The animal required to saccade to the target that matched the size or color of the cue, depending on the presented array. Most cues were presented on the computer screen, and a small fraction via electrical stimulation. Preliminary results from one animal suggest that phosphene size is approximately 0.5 degrees across, and that phosphene color is stable but varies from electrode location to location.

We conclude that the LGN presents a target for a visual prosthesis with substantial potential for additional investigation.

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CHRONIC HUMAN TESTING OF NERVE CUFF ELECTRODES FOR AN UPPER EXTREMITY NEUROPROSTHESIS

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

1) Dept. of Biomedical Engineering, Case Western Reserve University
2) Deparment of Orthopedics, MetroHealth Medical Center
3) Cleveland VA Medical Center

Introduction: The overall objective of this project is to extend the benefits of Functional Electrical Stimulation (FES) and neuroprostheses to higher level tetraplegia (C1-C4). An injury at a high cervical 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. The hypotheses are that nerve cuff electrodes can selectively activate individual muscles, they are controllable and have stable, long term recruitment.

Methods: Four percutaneous spiral nerve cuff electrodes were implanted in one subject with high cervical spinal cord injury. Two 4-channel electrodes were implanted on the radial and musculocutaneous nerves and two single channel electrodes were implanted on the suprascapular and axillary nerves. Tetanic stimulation was used to measure the force producing capabilities muscles in different positions. Percutaneous EMG recordings were used to evaluate selective activation of individual muscles using both monopolar stimulation and current steering. Finally, twitch recruitment curves were collected at different times and compared to evaluate the stability of the recruitment properties (threshold, slope, maximum).

Results: Selectivity was evaluated on the radial and musculocutaneous nerves. In both cases, current steering improved selectivity of the electrode. Monopolar selective activation of the triceps was achieved through radial nerve stimulation. Tetanic force recruitment curves were generated at 7, 9, 12 and 14 weeks post implant. Twitch EMG recruitment curves were generated at 5, 8, 11 and 16 weeks post implant. Most recruitment curves had gradual recruitment and the thresholds over this time have remained stable.

Conclusion: This study presents data collected from the first chronic human implant of the spiral nerve cuff electrode in the upper extremity. Selective activation has been achieved in many of the innervated muscles and the recruitment curves show that the muscles should be controllable. After the 16 weeks of percutaneous cuff testing, the subject received additional electrodes in the arm and hand with implanted stimulators. Work is now being done to give her control of the entire arm.

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A Spinal Cord Computer Interface Based on Signals Extracted from Descending Tracts of the Spinal Cord

Abhishek Prasad and Mesut Sahin
Department of Biomedical Engineering, New Jersey Institute of Technology, NJ

Injury at the cervical region of the spinal cord results in the loss of skeletal muscle control from shoulders down and hence quadriplegia. There is great need for volitional command generation in quadriplegic individuals. As an alternative to the brain-computer interface (BCI), we are testing the feasibility of using the voluntary motor signals recorded from the rubrospinal tract (RST) of the cervical spinal cord as a means of generating the command signals.

Three Long Evans male rats (350-400g) were used in this study. A microelectode array assembly (Cyberkinetics, Inc, UT) consisting of 11 electrodes was chronically implanted into the dorsolateral funiculus at C6-C7 levels of the spinal cord. A custom-made, multi-contact, silicone substrate, subdural electrode was also implanted at C5-C6 level to test the feasibility of extracting the motor signals from the surface. A flexion sensor (Spectra Symbol, UT) was sutured to the tendons on both sides of the elbow joint on the dorsal aspect to measure the elbow joint angle. Recordings were done for face cleaning behavior of the animal as this behavior involves cyclic forelimb movements.

For subdural electrodes, signal from each lateral contact was subtracted from that of the corresponding medial contact to obtain differential signals. Correlation analysis was performed between the signals from the proximal and distal pair of electrodes within a 2ms sliding window to determine the delay from one pair to the other. Correlation values less than 0.7 were rejected. Positive delay indicated motor activity and the negative sensory. The calculated delay values demonstrated that both motor and sensory activity existed in the neural signals. Based on the delay, motor activity was readily separated from the sensory signals.

Principal component analysis (PCA) was performed on the neural recordings from the microelectrode array. Linear regression technique was used to reconstruct the elbow angle using the rectified-averaged version of the neural signals. Correlation coefficient was found to be 0.80 ± 0.05 for a data set comprised of 20 trials. The number of principal components that accounted for greater than 90% variance was 3.9 ± 1.4. This suggested that with 11 electrode shanks, nearly four principal components, i.e. command signals that are uncorrelated with each other can be obtained. These principal components can be used to control, for instance, four different parameters of a robot arm. The results of this study demonstrate that motor signals recorded from the rubrospinal tract can be utilized as a means of Spinal Cord Computer Interface (SCCI).

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Determining the Ideal Fiber Optic Tip Shape for *in vivo* Uncaging

Martin M. Przeworski, Ubong Ime Udoekwere, Yu-li Liang, Graham Ellis-Davies, and Simon Giszter
Neurobiology and Anatomy, Drexel College of Medicine, Philadelphia, PA

Simulations and experiments indicate modest neural control can be achieved with a 50 um diameter uncaging probe in rat motor cortex. We are currently performing a fiber optic light guide characterization study in order to correlate the geometrical shape of the fiber optic tip with its light scattering profile and the computational model of this profile within cortical tissue. This will allow us to determine the area of light scattering in conjunction with the laser power necessary to achieve complete photolysis of a caged neurotransmitter. Our goal is to improve the excitation or inhibition of a set of target neurons. In this manner we can identify a safe region of operation of the laser, coupled to the fiber optic, that will uncage a target proportion of the neurotransmitter over a spatial domain in the dendritic trees of target neurons without damaging any of the target neurons within the tissue.

We begin by pulling one end of a 100 um quartz fiber optic cable with a standard laser pipette puller configured to pull fiber optics. In this way we change the cylindrical shape of the fiber into a right cone with a varying opening angle. We couple one end of the fiber to a high power solid state UV laser operating at a wavelength of 355 nm, and place the pulled end of the fiber normal to and a fixed distance from a CCD camera sensitive to UV light. We then record the light emitted from the fiber while incrementally varying the distance between the fiber's tip and the camera to generate a 3D reconstruction of the laser beam profile.

Since we know both the attenuation of the cortical tissue as well as the damage threshold of the target neurons, we can determine the ideal geometrical shape of the fiber's tip along with the operational power range of the laser necessary to achieve localized uncaging of the neurotransmitter and control without damaging the target neurons. This work has been supported by NSF grant NS 44564.

Investigation of Poly(3,4-ethylendioxythiophene) for Neural Stimulation Application

[1]Aditi Ray, [2]Jeffrey L. Hendricks, [3]John J. Whalen, [2]David C. Martin and [1,3]James D. Weiland
[1]Department of Biomedical Engineering, University of Southern California CA
[2]Department Biomedical Engineering, University of Michigan, Ann Arbor MI
[3]Doheny Retina Institute, Doheny Eye Institute CA

For any neural stimulator, an integral part of the device is the electrode material. Traditionally platinum and iridium oxide have been used as electrode materials. The present study focuses on testing conductive polymers as possible neural stimulation materials. Specifically, it studies the electrochemical properties of Poly(3,4-ethylenedioxythiophene), popularly known as PEDOT when used as stimulation material for medical devices. PEDOT was electrochemically deposited on to gold and iridium electrode sites on neural probes developed by Center for Neural Communication Technology, University of Michigan. The deposition was carried out for different durations to result in different coating thicknesses. On each neural probe at least one electrode site was left bare for control study. The entire deposition process was done by Prof. David Martin and his team at University of Michigan, Ann Arbor. Impedance and cyclic voltammograms were taken for each PEDOT coated electrode and compared to that of the bare electrode. Each of the coated electrodes was also stimulated by a series of single pulses, each a particular combination of pulse duration and current amplitude. The stimulus pulses were designed with either 0.1 ms, 0.5ms or 1 ms pulse duration, cathodic-first and charge-balanced. Current amplitudes were applied to maintain charge per phase value as 10, 20, 30, 40 and 50 nC. The response to each of the stimulus pulse was compared across electrodes coated with different thicknesses of PEDOT and also against the bare electrodes. All tests for conducted in 0.1 M phosphate-buffered saline solution at room temperature. Measurements were made using a platinum counter electrode and silver-silver chloride reference electrode.

The impedance of all coated electrodes was found to be at least a decade lower than that of the bare electrode. Cyclic voltammogram traces showed the total charge carrying capacity of the coated electrodes was larger than that of the bare electrodes. Analysis of the voltage responses of each electrode to each of stimulus pulses revealed a window of optimal performance. Electrodes coated with 6 μC of PEDOT had a voltage drop of -3.31 V in the cathodic phase of 100 μA, 0.5 ms stimulus pulse while the uncoated electrodes had a voltage drop of 3.88 V for the same stimulus pulse. Preliminary results indicate that a coating thickness of 6 μC of PEDOT exhibits the best voltage response to the applied stimulus pulses as compared to that of the bare electrodes.

Laser stimulation of the auditory nerve stimulation is possible at high repetition rates

Philip Littlefield 1, Agnella D. Izzo 2, Joseph T. Walsh 2, Jr., E. Duco Jansen 3, Jim Webb 4, Heather Ralph 4, and Claus-Peter Richter 1

1 *Department of Otolaryngology, Feinberg Medical School, Northwestern University, Chicago, IL*
2 *Department of Biomedical Engineering, Northwestern University, Evanston, IL*
3 *Department of Biomedical Engineering, Vanderbilt University, Nashville, TN*
4 *Aculight Corporation, Bothell, WA 98011*

In neural prosthesis development, particular success has been realized with cochlear implants. These devices bypass damaged hair cells in the auditory system by direct electrical stimulation of the auditory nerve. Stimulating discrete spiral ganglion cell populations in cochlear implant users' ears is similar to the encoding of small acoustic frequency bands in a normal-hearing person's ear. In contemporary cochlear implants, however, 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 stimulate smaller populations of spiral ganglion cells. Recently, we have demonstrated that spatially selective stimulation of the cochlea is possible using light.

The present experiments demonstrate that high repetition rates of laser stimulation are possible in the cochlea. Compound action potentials were recorded with a gross electrode placed at the round window and single auditory nerve fibers activity was recorded with fine glass pipettes from the auditory nerve at the meatus acousticus internus. Stimulation was made with an fiber-coupled diode laser (Aculight). The wavelength was between 1.844 and 1.873 µm and the pulse duration was 10 µs. Repetition rates could be selected between 2 Hz and 1 kHz. The laser output was coupled to a 200-µm diameter optical fiber, which was placed through the round window, opposite to Rosenthal's canal.

Compound action potential peak-to-peak amplitudes remained constant over extended periods of stimulation. At present, continuous stimulation occurred up to six hours and with up to 50 Hz in repetition rate. Single fiber experiments were made using repetition rates of up to 1 kHz. Action potentials occurred 2.5-4 ms after the laser pulse. Maximum rates of discharge were up to 250 action potentials per second. With increasing stimulation rate (>300 Hz), the action potentials did not respond strictly after the light pulse.

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Electrical Stimulation of the Orbicularis Oculi for Eye-blink Restoration

Nicholas A. Sachs 1,2 , Eli L. Chang 2,3 , James D. Weiland 1,2,3
1 Department of Biomedical Engineering, University of Southern California, Los Angeles, CA
2 Doheny Eye Institute, University of Southern California, Los Angeles, CA
3 Department of Ophthalmology, University of Southern California, Los Angeles, CA

Dysfunction of the seventh cranial nerve often results in facial paralysis and loss of the ability to blink the eye. Without adequate treatment this can lead to corneal scarring, diminished vision, and potential loss of the eye.

Current methods for preserving the cornea and/or ensuring eye closure following facial paralysis include the use of artificial tears, the implantation of gold weights or mechanical springs in the eyelid, nerve and muscle transfer, and tarsorrhaphy. All of these are helpful in preserving the eye although none of these techniques, even used in combination, are fully effective. Additionally, these techniques are often inconvenient, subject the patient to multiple surgical procedures, and are cosmetically unacceptable. Electrical stimulation of the orbicularis oculi muscle has the potential to provide a more elegant and effective method for eliciting eyelid closure.

This study investigated the use of electrical stimulation of the orbicularis oculi muscle as a means of restoring blink function. An animal model of orbicularis oculi paralysis was created by sectioning the seventh cranial nerve in rabbit. Twenty paralyzed and five normal rabbits were acutely implanted with a subcutaneous stimulating electrode near the margin of the upper eyelid. Biphasic current controlled stimulation pulses were delivered between contacts implanted at the medial and lateral edges of the eyelid.

Strength-duration curves for lid twitch threshold were generated, and quantitative measurements of lid closure were made for systematically varied parameters including pulse amplitude, pulse width, number of pulses delivered, and duration of paralysis prior to stimulation. Normal rabbit achieved the greatest degree of lid closure, followed by paralyzed rabbit demonstrating evidence of at least partial reinnervation and paralyzed rabbit demonstrating persistent denervation, respectively. Trains of 10ms biphasic pulses delivered at 50Hz were found to be the most effective means of eliciting lid closure for the range of parameters tested.

Future studies will investigate the effects of chronic stimulation, as well as methods for decreasing the amount of current necessary to achieve lid closure. Possible strategies being considered include the use of multiple stimulation channels, promotion of reinnervation in the paralyzed muscle, and the use of triggered stimulation to provide a synchronous blink with the contralateral side.

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Extraction of Cardiac Parameters from Vagus Nerve Recordings

Marcia A. Pool[1] and Mesut Sahin[2]

[1]*Department of Biomedical Engineering, Louisiana Tech University, Ruston, LA, USA*

[2]*Department of Biomedical Engineering, New Jersey Institute of Technology, Newark, NJ, USA*

Heart rate is continuously varying depending on the amount of activity being performed or the emotional state of an individual. Heart rate, atrioventricular (AV) conduction time, and contractility are all important parameters that are controlled by the autonomic nervous system. Specifically, we are concerned with determining if the cardiac parameters can be extracted from the parasympathetic nervous system via the vagus nerve. Whole vagus nerve discharges were recorded using very small cuff electrodes with two platinum contacts with a separation distance of 1 mm and a very low noise amplifier. Baseline recordings were taken before bi-lateral carotid artery occlusion was performed to alter heart rate. Data obtained from these experiments was first processed for frequency content; then, the motor signal was extracted from the whole nerve recordings using the correlation method. Finally, the motor signal was correlated to the variations in the heart rate. Consistent correlation values were obtained for baseline recordings as well as for occlusion recordings. The mean correlation value obtained for baseline recordings was -0.79±0.20, and the mean correlation value obtained for occlusion recordings was -0.72±0.20.

Floating Light Activated Micro-Electrical Simulators: Modeling and In Vivo Testing

Mesut Sahin[1], *Mustafa Patan*[1], *Arthur Che-An Wu*[2], *and M. Selim Unlu*[2]
[1]*Biomedical Engineering Department, New Jersey Institute of Technology*
[2]*Electrical and Computer Engineering, Boston University*

Tethering forces of the interconnects induce mechanical stress on implanted neural electrodes and thus cause chronic tissue response for long term implants. A floating micro-stimulator activated via wireless means is one possible method for eliminating the interconnects. As a method of energy transfer to the micro-stimulator, a laser beam at near infrared (NIR) wavelengths can be used where the penetration depth into the neural tissue is much better than that of the visible spectrum. In this project, our main objective is to design a Floating Light-Activated Micro-Electrical Stimulator (FLAMES) that is capable of activating sufficient neural tissue around it to generate a functional response. Such a floating micro-stimulator can find many neuroprosthetic applications in the central nervous system.

As the first step to device optimization, we developed a comprehensive model that included optical transmission characteristics of neural tissue, light-to-current conversion by the micro-stimulator, electrode-electrolyte properties at the contacts where the current leaves the device, and voltage field generated by the current in the volume conductor around the device. The potential field in the volume conductor was simulated with a finite element model. The properties of titanium nitride as a contact material were studied independently with a current pulsing method for various electrode sizes and bias voltages. Optical scattering, reflection, and absorption properties of the neural tissue were predicted using the empirical data from literature. Energy conversion efficiency of the prototype devices were measured experimentally. All the experimental and simulation data were incorporated in a software code written in Matlab platform.

The Matlab routine iteratively calculated the optimal device active area for light collection and the contact areas to minimize the overall device size while maximizing the voltage field in the volume conductor. Maximum exposure limits for infrared lasers (300 mW/cm^2), frequency of pulsing, and pulse width were also factored into the model. Several devices to meet the requirements of different neural stimulation applications were designed. Details of this analysis will be presented at the workshop.

The prototype devices were also tested on the rat sciatic nerve for their stimulation strength at various implantation depths. The thickness of the tissue above the micro-stimulator, thus the distance that the laser beam traveled, was varied. The NIR threshold for activation was measured for increasing pulse widths and the strength-duration curve was obtained for various thicknesses of the neural tissue. The initial tests with prototype devices demonstrated that stimulation at depths of as much as 3.5 mm is feasible with a laser beam strength of $0.6mJ/cm^2$ for pulse widths of 40-90μs. The current efforts in this projects are concentrated on fabrication of a new generation of devices with smaller sizes and multiple PN junctions in series to increase the output voltage.

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Selectively Stimulating the Human Femoral Nerve with a Flat Interface Nerve Electrode

Matthew A. Schiefer[1,2,3], Ronald J. Triolo[1,2,3], Dustin J. Tyler[1,2,3]
1. Department of Biomedical Engineering, Case Western Reserve University
2. FES Center of Excellence, Cleveland VAMC
3. APT Center of Excellence, Cleveland VAMC

Spinal cord injuries (SCIs) significantly reduce an individual's independence and quality of life. Restoration of standing ability could significantly increase mobility and independence while significantly decreasing bone loss and the occurrence of pressure ulcers. Neuroprostheses have restored standing and stepping in some individuals. To reduce fatigue and improve standing ability, a computer modeling study was undertaken to develop the next generation Flat Interface Nerve Electrode (FINE), which will have a minimal number of optimally positioned contacts to selectively activate muscles of the thigh. No *a priori* knowledge of fascicular distribution is assumed.

Digitized images of human femoral nerve cross sections were traced and extruded to create 3D finite element models. A FINE was modeled as a silicone cuff enclosing the nerve. Simulations were run with a cathodic square pulse, generating spatial voltage distributions that were imported to MATLAB and interpolated along randomly positioned and sized axons. Each axon was modeled in NEURON. Selectivity, defined as the difference in the percentage of target and non-target axons that were activated, was determined in MATLAB.

In all models, a selectivity of at least 60% was achieved for each muscle with 1 optimally positioned contact for that muscle. Average selectivity was 69% when the FINE's opening height was 3.8 mm. A 40% reduction in opening height (2.3 mm) increased selectivity to 79%. Thus, by slightly reshaping the nerve and bringing stimulating contacts in close proximity to target fascicles, individual muscles were selectively activated. Near-simultaneous use of 2 contacts increased selectivity in 82% of models, although rarely was the increase statistically significant.

This work was supported by the Department of Education GAANN Training Grant in Neural Engineering, NIH contract RO1-EB001889-01 and the Advanced Platform Technology (APT) Center of the US Department of Veterans Affairs. Simulations were run at the Ohio Supercomputing Center.

Ultra-Fine Structures on Neural Probes Reduce Cellular Encapsulation

John P. Seymour[1] and Daryl R. Kipke[1,2]

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

Topic: Materials and Devices

The objective of this study is to investigate the tissue response to a neural-probe design with subcellular-sized structures and optimal electrode placement. The implemented parylene-based probes have both a stiff penetrating shank (42 μm by 70 μm) and fine structures (as small as 4x5 μm) that form a lattice-like architecture lateral to the shank. Our experiments verify that, despite using a flexible substrate and small dimensions, these devices are mechanically robust and practical as neural probes. *In vivo* testing was conducted with seven Sprague-Dawley rats, each implanted with four neural probe geometries (4-, 10-, 30-, 100-μm features) in the motor cortex for 4 weeks. Reactive responses were assessed by immunohistochemistry for GFAP (astrocytes), OX42 (microglia), NeuN (neurons), and laminin. The neuronal loss was significantly reduced by twofold ($p<.01$) around the 4x5 μm feature relative to larger probe shank in the first 25 μm around the interface. In the same region, non-neuronal cell density was significantly reduced relative to the probe shank in all designs but the 10x5-μm feature. Additionally, laminin+ and OX42+ tissue showed greater intensity and thickness around the shank, indicating that the scar formation typical of cortical implants was mitigated at the thin lateral structure. These results suggest that using MEMS-based microfabrication to create subcellular structures and lateral placement of the electrode sites should significantly reduce encapsulation in the rat neocortex, and provides a new design space for neural probes.

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Neuroprosthetic Effect of Peroneal Nerve Stimulation in Multiple Sclerosis

Lynne R. Sheffler[1,3], Maureen T. Hennessey[1,3], Gregory G. Naples[1,3], and John Chae[1,2,3]

[1]Departments of Physical Medicine and Rehabilitation and
[2] Department of Biomedical Engineering
[3]Department of Physical Medicine & Rehabilitation, MetroHealth Medical Center \ Case Western Reserve University, Cleveland, OH

Topic: Sensory-Motor and Functional Electrical Stimulation

Dorsiflexion and eversion weakness are common neurological manifestations of multiple sclerosis and can contribute significantly to physical disability. The use of functional electrical stimulation to augment motor activity and improve function and quality of life in patients with various upper motor neuron diseases has been extensive. The specific clinical, functional, and biomechanical impact of peroneal nerve stimulation (PNS) to correct for dorsiflexion and eversion weakness in the multiple sclerosis patient population, however, has not been previously described. The objectives of this study are: (1) to quantitate the neuroprosthetic effect of PNS in correcting for dorsiflexion and eversion weakness in multiple sclerosis; (2) determine if there is a sustained or enhanced neuroprosthetic effect of the peroneal nerve stimulator on functional mobility with extended usage; and (3) to explore the possibility of a motor relearning effect secondary to PNS. Eleven subjects with multiple sclerosis and evidence of unilateral dorsiflexion and eversion weakness utilized the Odstock Dropped Foot Stimulator (ODFS), a surface peroneal nerve stimulator, on a daily basis for a 4-week time period. The subjects underwent functional ambulation testing using the Timed 25-Foot Walk (T25-FW) portion of the Multiple Sclerosis Functional Composite (MSFC) and the Modified Emory Functional Ambulation Profile (mEFAP) at baseline and at 4 weeks post-intervention. A subset of subjects was then asked to undergo quantitative gait analysis with treadmill analysis to compare temporospatial variables and kinematic and kinetic measurements of PNS as compared to no device. A series of paired T-tests was performed to compare the ODFS to no-device conditions. At baseline, there was no significant difference between conditions based on either measure. However, after 4 weeks of usage, there was a trend toward significant difference between conditions in favor of ODFS for the obstacles ($p=.087$) and stair climbing ($p=.068$) portions of the mEFAP. The T25-FW was not significantly different between conditions at 4 weeks. There was no evidence of the motor relearning effect after 4 weeks of usage. Individual kinematic and kinetic data derived from quantitative gait analysis with treadmill walking on a subset of subjects will be reviewed.

Conclusions: The neuroprosthetic effect of PNS may consist of a functional and biomechanical enhancement of gait for multiple sclerosis patients with dorsiflexion and eversion weakness. The greatest functional benefit may be evident in those activities that require significant steppage ability, such as stair climbing and negotiation of obstacles. Further studies investigating both the neuroprosthetic impact of PNS on functional ambulation and the broader application of functional electrical stimulation on motor impairment related to multiple sclerosis are indicated.

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Laser Micro-Machined Multi-Channel Stimulating and Recording Electrode Arrays

Suwas Nikumb[1], Craig Dinkel[1], Mandar Jog[2], Jessie Y. Shen[3], Souhile Assaf[3]

[1]Integrated Manufacturing Technology Institute, National Research Council Canada, London, ON
[2]Department of Clinical Neurological Sciences, University of Western Ontario, London, ON
[3]Medtrode Inc., 700 Collip Circle, London, ON

Background: Micro-machining techniques enable the fabrication of miniature features which are required to build viable multi-channel electrode arrays. The well researched application of deposition technology to build conductor tracks on dielectric substrates often has difficulties producing robust conductor tracks when the track thickness falls below 0.05 mm. Problems include variance in thickness and breaks in the track.

Laser micro-machining is a precision fabrication technology that cuts the conductor tracks out of commercially available conductor sheets, such as platinum, gold, titanium, platinum iridium, etc. This approach offers better consistency in thickness and the resulting conductor tracks do not have contamination issues incurred in deposition technology.

Methods: Laser cutting defines the stimulating and recording conductor tracks such that they are customized for power efficiency and signal integrity through parameters such as sheet thickness, track width, and contact surface area. Commercially available sheets currently limit track thickness to approximately 10 microns and track width to 20 microns. After the conductor is thermo-bonded to dielectric backbone(s), depth machining etches in the finer details and laser cutting separates each electrode from its neighbors. Electrodes are then assembled into arrays optimally configured for specific applications. In particular the array configurations are designed to realize certain spatial arrangement of the contacts. For instance cortical electrode grids combining stimulation and recording poles arranged in a non-planar configuration are ideal for recording and pacing neurons in a volume of brain tissue.

Results: We are currently testing prototypes configured for deep brain stimulation which combine the intra-operative recording features on implantable multi-channel electrode grids formed from Platinum bonded on polyimide. This configuration can be easily scaled up to 64 channels. The pole sizes for stimulating and recording electrodes are 2513μm^2 and 250μm^2, respectively. The average impedances of the recording and stimulating channels at 1kHz are 7800Ω and 320Ω, respectively. Currently the yield on individual electrodes is approximately 70%. Assembled array has poles vertically spaced between 200µm to 1mm and horizontally staggered around 500µm. Compared to current DBS electrodes, these micro-electrode arrays have smaller contact areas and higher pole density, which enables more configurable stimulation fields and more comprehensive target localization data.

This work was supported by Proof of Principle Grant (POP-) by Canadian Institutes of Health Research (CIHR) and Medtrode Inc.

Optical Interfacing with Populations of Retinal Ganglion Cells – Preliminary Studies

Nairouz Farah, Inna Reutsky and Shy Shoham

Faculty of Biomedical Engineering, Technion – Israel Institute of Technology

Neuroprosthetic retinal interfaces for degenerative diseases of the outer-retina depend upon the ability to bypass the damaged photoreceptor layer and directly activate populations of retinal ganglion cells. Current approaches to this task largely rely on an electrode array implant that will lie on the epi-retinal or sub-retinal surface. Alternative approaches could be achieved by direct light-based activation of the retinal ganglion cells (RGCs). In addition to being non-contact, optical techniques lend themselves relatively easily to a variety of technologies for achieving patterned stimulation with high temporal and spatial resolution.

We will present preliminary in vitro results using two strategies for performing direct light activation of RGCs: 1) Patterned uncaging of caged glutamate[1]. 2) Activation of Channelrhodopsin II, a light-gated cation channel that can be artificially expressed in RGCs[2]. Our approach attempts to achieve controlled large-scale, flexible stimulation of the retinal tissue with single-cell resolution and high temporal accuracy through adaptations of video projection technology.

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Chronic InVivo *Recordings With a New Implantable, Wireless Neural-Recording Array*

Florian Solzbacher[1], M. Töpper[1,2], L. Reith[1], P. Tathireddy[1], S. Kim[1], M. Klein[2], and H. Reichl[2]

[1]Microsystems Laboratory, Department of Electrical Engineering, University of Utah, Salt Lake City, UT
[2]Fraunhofer Institute for Reliability and Microintegration IZM, Berlin, Germany

A wireless neural interface for chronic recording has been developed for use in the central and peripheral nervous system and successfully tested in mammalian cortex for a period of over 1 month. The interface is based on the concept of the Utah Electrode Array (UEA). It consists of a 10x10 microelectrode array, an 88-channel signal amplifier, data compression, RF communication, power recovery module, alternatively 1 or 2 60-turn planar coils (Au on Polyimide) on a ferrite substrate, and surface-mount device (SMD) components. The system is assembled by AuSn flip-chip bonding of the IC as well as SMD, coil, and ceramic spacer on the array platform. The precise description of this biocompatible integration concept was already published. We will present data demonstrating the design and functionality of the device.

The objective of this work was to develop a new, chronically implantable, wireless neural-recording interface that will allow recording function for at least 1 year of operation. In order to accomplish this task, we have developed a new packaging concept, based on the existing UEA. The UEA is used as a mechanical platform and electrical re-rerouting plane for a signal processor (including 88 amplifiers, D/A converter, spike detection, power regulator, and RF telemetry link for received commands and transmitted neural data [88 channels spike data + 1 streaming channel at 15 kSamples/s]), SMD components, a Polyimide/Au-based thin-film coil, and ceramic spacers. The components are assembled on the modified UEA platform chip using AuSn flip-chip bonding/soldering. The devices are encapsulated using SiC and Parylene thin-film layers. We will show fully integrated and packaged devices as well as a hybrid version connecting a conventionally wired UEA to the signal processor. We will also present 1 month of neural action potential data of the wireless transmission system in comparison to a benchmark Cerebus system, including principle component analysis for select channels.

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Local Delivery of CNQX by Conducting Polymer Electrodes to Cultured Neural Networks

William R. Stauffer [1,2], *Xinyan Tracy Cui*[1,2,3]

1. Department of Bioengineering, University of Pittsburgh, Pittsburgh, PA
2. Center for the Neural Basis of Cognition, University of Pittsburgh, Pittsburgh, PA
3. McGowan Institute for Regenerative Medicine, University of Pittsburgh, Pittsburgh, PA

Cultured neural networks on microelectrode arrays have been utilized as tools for the detection of toxins and drugs, as models of cortical network function, and as possible agents of intelligent control for robotic devices. Previous technological advances have allowed for an electrical stimulus to be applied in a very controlled, precise fashion. This has led to exciting insights about the behavior of neural networks. On the other hand, most chemical stimulation or modification of network activity has relied on bath addition of the chemical so the effects are network-wide. While significant insights have been gained through this mechanism, more could be learned if given the ability to apply these chemicals in a controlled, local fashion.

In this work a novel conducting polymer-mediated controlled delivery of the AMPA (α-amino-5-hydroxy-3-methyl-4-isoxazole propionic acid) receptor antagonist CNQX (6-cyano-7-nitroquinoxaline-2,3-dione) is presented. AMPA receptors are CNS glutamate receptors that mediate fast synaptic transmission. CNQX was successfully incorporated into the conducting polymer polypyrrole (PPy) and shown to release, on electrical command, into solution. It is shown that the amount of CNQX released can be controlled by the number or duration of electrical pulses. The CNQX/PPy films were synthesized on the electrodes of a 64 channel multielectrode array (MED64, Panasonic) and murine cortical neurons were cultured. Neural activity was sampled at 20Khz. Spike sorting was performed using Offline Sorter (Plexon). Spontaneous network activity was present at 5 DIV, and network wide bursting was present by 10 DIV.

Network recordings were taken before and after electrochemical release of CNQX. The drug was released from 8 conducting polymer electrodes by cycling the potential of the electrodes from -.8V to .6V eight times. After release, network bursts were reduced in frequency from .3 to .1 Hz. Individual unit activity was lessened or abolished within 200μm of a releasing electrode. After changing the media out, network activity returned to baseline. In future work the technique will be refined to gain better and finer control over drug release, as well as modifying culture density, until it is possible to inhibit the response of single cells within the network. This tool can then be utilized to experimentally investigate the role of individual cells in complex network behavior.

Developing Brain- and Non-Brain-Based Command Options for an Upper-Limb Neuroprosthesis

Dawn Taylor[123], Holle Carey[1], Andy Cornwell[1], Thomas Cowan[1], Stephen Foldes[1], Amar Marathe[1], Abirami Muralidharan[1], Ben Rellinger[1], Michael Stetner[1]

1) *Dept. of Biomedical Engineering, Case Western Reserve University*
2) *Louis Stokes Cleveland VA Medical Center*
3) *Dept of Neuroscience, Lerner Research Institute, Cleveland Clinic Foundation*

We are evaluating command sources for controlling functional electrical stimulation (FES) systems designed to restore arm and hand movements in individuals with high tetraplegia. Ideally, we would like to be able to accurately extract the desired limb movements from the natural brain patterns generated when a spinal cord injured person attempts to move. However, with current technologies, especially non-invasive technologies, it is unlikely that we will be able to perfectly decode the available neural signals into the desired complex upper-limb movements. Therefore, the question becomes-- ***'How can we restore the most function using the command signals available to the user?'***

Our strategies for maximizing function include: 1) maximizing the natural movement information extracted from the brain, 2) retraining the brain to produce additional information in a way that will start to feel natural with continued practice, and 3) combine what we get from the brain with other non-brain-based command options such as EMGs and/or more traditional assistive device options.

Maximizing information extracted: We have developed software that enables real-time control of a virtual hand (i.e. X, Y, & Z position, hand open/close, and various wrist rotations). We can now test how well intracortical unit activity and local field potentials can be used to simultaneously control all needed degrees of freedom to make full use of the upper limb neuroprosthesis.

Retraining the brain to produce more information: We have further refined our coadaptive decoding algorithm to include a non-linear transformation stage. This has facilitated the learning of new more-useful command strategies.

Combining brain and non-brain-based commands: Currently, participants in the upper-limb neuroprosthesis study control their arm movements using signals recorded from EMG electrodes chronically implanted on various muscles of the head and neck. We have now shown that a single external electrode placed over the hand area of sensorimotor cortex can be used to acquire both EEG and EMG signals simultaneously, and that subjects can use this one electrode to generate two-dimensional movements of a virtual arm. This opens up the possibility of increasing the available command signals in future neuroprosthesis users by strategically implanting EMG electrodes over areas where useful EEG signals can be detected as well.

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Sensory and Motor Mapping of Rat Cortex

Thompson, Aiko, Smith, KL , Chen, L , Chen, XY , Carp, JS , Wolpaw, JR Shain, W
Wadsworth Center, NYS Depart. of Health, Albany, NY

Consistent placement of intracortical electrode arrays requires accurate maps of cortical sensory and motor representations. The extent and characteristics of inter-animal variation remain unclear. To assess this variation, we mapped lower limb sensory and motor representations in adult male Sprague-Dawley rats.

A section of skull over frontoparietal cortex (typically 0.5 to 4.5 mm lateral and -2.0 to +9.0 mm posterior to bregma) was removed. The dura remained intact. A tungsten microelectrode was used for stimulating and recording from the cortical surface. To generate sensory maps, single square pulses were delivered to the contralateral posterior tibial nerve via a nerve cuff. Eight sensory evoked potentials (SEPs) were averaged from each site. To generate motor maps, stimulus trains were delivered to the cortical surface and motor evoked potentials (MEPs) were recorded with pairs of fine-wire EMG electrodes in the contralateral triceps surae muscles. Each map was generated using 0.5-mm steps across the exposed cortical surface. Up to 95 sites were used for each map. To verify the surface results, depth recordings were performed in several rats at the end of the experiment.

Sensory maps were obtained from 12 rats. The maximum SEP varied from 0.48-5.40mV peak-to-peak and was typically focused 2.0-3.0 mm lateral to the midline and 0.5-2.0 mm caudal to bregma (in agreement with Hall and Lindholm (Brain Res. 66:23-38, 1974)). Motor maps were obtained from 16 rats. The maximum early MEP varied from 0.09-2.49 mV. The location of the motor focus was more variable than that of the sensory focus, and was often more posterior than expected.

These data reveal substantial inter-animal variation. Thus, sensory and motor mapping of the cortical surface is needed for each rat prior to insertion of long-term intracortical recording or stimulating devices.

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Planning for the Implementation of an Intracortical Visual Prosthesis

Philip R. Troyk[1], D.Bradley[2], M.Bak[8], S.Cogan[4], R.Erickson[2], C.Kufta[5], D.McCreery[6], E.Schmidt[7], V.Towle[2]. *[1]Pritzker Inst Biomed Sci & Eng, Illinois Institute Technology, Chicago, IL; [2]University of Chicago, Chicago, IL; [3]National Institute of Health, Bethesda, MD; [4]EIC Laboratories, Norwood, MA; [5]Frederick, MD; [6]Huntington Medical Research Institutes, Pasedena, CA; [7]Easton, MD, [8]Micro Probe, Inc, Gaithersburg, M.*

Within the past 5 years, there has been an explosion of visual prosthesis research, within the U.S. and worldwide. Most of these efforts target the retina as the location of an artificial interface between a camera-based imaging system and the human visual system. It is anticipated that, unlike the cochlear implant, hundreds or thousands of parallel stimulation channels will be required for a perceptually useful visual prosthesis. In general, for all approaches, the development of reliable implantable hardware and establishment of strategies for neural coding that will result in a clinically-significant visual substitution system remain unrealized. IIT leads a multidisciplinary team for the development of an intracortical visual prosthesis using large numbers of intracortical micro-electrodes that penetrate the visual cortex. The overall objectives of our multi-institutional team-based project are to advance the technology sufficiently to provide a reasonable expectation of reliability and safety for implantable hardware, to develop an animal model to perform crucial electrical stimulation studies, and to consider key ethical issues, so that a multi-model decision process about proceeding to a human volunteer can be defined and implemented.

Although considerable research had been historically supported by the NIH for the development of safe intra-cortical microelectrodes, our in-vitro and in-vivo testing of over 400 electrodes in bench electrochemical in-vitro models, and 3 different animal models, confirm that the in-vivo charge injection capabilities of commonly-used electrodes are significantly less than had been previously assumed. Our working hypothesis is that limitations in counter-ion availability, or mobility within the brain, impede the charge injection process. We have defined a new paradigm for defining the safe charge injection limits based upon potential excursions of the electrodes during stimulation, rather than *apriori* definitions of charge injection capacity. Using this new electrode qualification process, we are presently assessing a modified electrode design that would be suitable for human implantation. These results transcend our cortical visual prosthesis project and affect all neural prosthesis research.

Although the prospect of human implantation for an intracortical visual prosthesis has often seemed uncertain, we have made significant progress in understanding how a first-generation system will be configured. We have developed self-contained 16-channel wireless modules that use new methods of electrode array assembly, as well as our design for an application-specific-integrated-circuit that drives the microelectrodes using a rule-based protection method. In a first volunteer, we plan to implant 3-4 of these modules in order to establish the stability of the artificial neural interface. Once the stability of the neural interface has been demonstrated, it seems feasible to perform an additional surgical procedure to provide the volunteer with additional modules, up to approximately 1000 electrodes, that would cover the surface of the occipital pole.

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Pelvic robotic rehabilitation and BMI applied in the SCI and intact rat

Ubong Ime Udoekwere 2, Corey B. Hart 1, Lollise Mbi 1, Simon F. Giszter 1
1 Neurobiology and Anatomy, Drexel College of Medicine, Philadelphia, PA
2 School of Biomedical Engineering, Science and Health Systems, Drexel University , Philadelphia, PA

Ultimately our goal is to implement a closed-loop Brain Machine Interface (BMI) that has the capability of providing real-time control of the robot assistive forces on the pelvis for neurorobotic rehabilitation of injured rats. About 20% of postnatal day1-2 rats spinalized in the thoracic segments (T9-T10) are capable of significant hind-limb weight support as adults, and our previous experiments strongly support a major role for cortical control of the mid/low trunk muscles in such recovery. Based on this rationale we examined robotic rehabilitation and assessment of spinalized rats, using robot applied forces at the level of the pelvis to attempt to train trunk muscle control to integrate with lumbar CPG and thereby improve the rats weight support. We are able to achieve manipulation of the lumbar region with a cantilevered robotic arm attached to the rat's pelvis via a surgically implanted pelvic orthosis. We have now tested a functioning BMI real-time system to control the cantilevered robot. This includes a Cyberkinetics Cerebus neural recording system which sends 256 bits of spike data on 128 channels to the Phantom robot system every 1ms. These packets are used for the BMI, with the option of successively triggered or continuous control of the algorithms that drive the robot. The system also allows us to obtain kinematic and kinetic information via the robot, OPTOTRAK, and ATI 6 axis force transducer.

Currently our focuses are: (1) to understand the responses of spinalized adult rats to the assistive interactions of the robotic apparatus without the closed-loop neural control. This is a necessary prelude to our eventual goal of BMI. (2) to explore the biomechanical responses and neural adaptation of intact rats to closed-loop BMI neural driven control of the robotic assistance. (3) to apply open-loop rehab and closed-loop BMI in spinal injured rats.

Preliminary data from our robotic rehabilitative training on adult injured rats show that pelvic force application can provide training leading to significant functional improvement and can supply the investigator with novel biomechanical data. Also, preliminary data in intact rats show that rats may adapt firing rates in hindlimb /trunk motor cortex in response to fixed or closed loop neurorobotic forces at the pelvis.

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Deciding on DBS for Parkinson's Disease:
Patient, Carepartner and Clinician Perspectives

Dorothy E. Vawter [1], Angela W. Prehn [1], J. Eline Garrett [1], Karen G. Gervais [1], Timothy Q. McIndoo [1], and Raymond G. DeVries [2]

1 Minnesota Center for Health Care Ethics, Minneapolis, MN
2 St. Olaf College, Northfield, MN

Topic area: Deep Brain Stimulation

Decisions to have deep brain stimulation (DBS) for Parkinson's disease (PD) can be complex. How able are persons with advanced PD to make informed DBS decisions? What information and other supports do they value? How satisfied are they with the DBS decisionmaking process?

Twenty-eight persons with DBS for PD (patients), 19 carepartners and 48 surgical researchers in movement disorders (clinicians) participated in 12 focus groups (4 of patients, 3 of carepartners, 5 of clinicians) and 2 in-depth interviews (2 clinicians). All were asked about the experience of deciding to have DBS, including patients' ability to make informed decisions and the types of information and support they value. Patients and carepartners were also asked about their level of satisfaction with the DBS decisionmaking process.

Although the decision to have DBS was easier for some patients than others, patients, carepartners and clinicians agreed that persons medically eligible for DBS for PD can make informed decisions about whether and when to have DBS. None believed that advanced PD precludes informed DBS decisionmaking. Clinicians noted that PD patients (without dementia) are among the best informed patients. Most participants agreed, however, that the DBS consent process deserves additional attention.

Most patients and carepartners desired and relied on more information than they received from the DBS team(s) they consulted. They particularly valued the information received from persons with DBS, the device manufacturer's employees, the Internet and medical literature. In addition to valuing balanced and complete risk/benefit information—which which was essential to their decision whether to have DBS—patients valued information and support that helped them control risks, improve outcomes, alleviate anxiety and manage the experience. For example, they appreciated DBS teams that they perceived to be organized and caring; they wanted more support during microelectrode recording and electrode implantation; and they sought better preparation for the pulse generator surgeries, post-operative periods and programming activities.

Patients were resourceful and exhibited well-developed support systems and coping skills. The multiple sources of information and support that they and their carepartners tapped were extraordinary. It is not surprising that some patients struggled with synthesizing the information and applying it to their circumstances. By understanding

differences in the ease of DBS decisions and anticipating the types of information and support that patients and carepartners value, providers can enhance the informed consent process and assist patients to make DBS decisions they are satisfied with.

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Impedance characterization of deep brain stimulation electrode in vivo with sinusoidal and transient current responses

Xuefeng F. Wei, Warren M. Grill
Department of Biomedical Engineering, Duke University, Durham, NC

The therapeutic efficacy of deep brain stimulation (DBS) is affected by local charge delivery to specific populations of neurons. Charge delivery can occur through capacitive (non-Faradaic) charge transfer or resistive (Faradaic) charge transfer, which may contribute differently to tissue damage and electrode corrosion. The objective of this research is to quantify the composition of the charge transfer by characterizing the impedance of DBS electrode following acute implantation in cat brain.

We used a 3-electrode system to measure the impedance of the electrode-tissue interface using sinusoidal currents and charge-balanced biphasic current pulses. The impedance was represented by the parallel combination of a Faradaic charge transfer resistance (R_f) and a double layer capacitance (C_{dl}) in series with an access resistance (Rs). Impedance spectrograms were measured over the frequency range from 1Hz to 100 kHz for sinusoidal currents, and voltage waveforms across electrode-tissue interface were measured for pulsed currents. R_f and C_{dl} as a function of current density were determined by fitting the impedance spectrograms and voltage waveforms to the responses of a three-element linear circuit model.

For both sinusoidal and transient responses, the Faradaic resistance was nonlinear with current density, with higher current densities associated with smaller R_f. Because of the non-uniform current density distribution on the electrode surface, the resistive (Faradaic) charge transfer was space dependent with more charge transferred across the electrode edges. The voltage transient response to current pulses was consistent with the response of a parallel RC circuit with the capacitive current dominating during the high frequency (transient) phase of the pulse and the resistive current increasing during the low frequency (steady state) phase of the pulse. Therefore, the composition of charge transfer (resistive vs. capacitive) varied both spatially along the electrode surface and temporally during the course of the stimulating pulse.

Characterizing the impedance of the DBS electrode-tissue interface provides understanding of the fundamental mechanisms of charge injection at the electrode-tissue interface and is important to the design of new generation electrodes that reduce the propensity for tissue damage or electrode corrosion.

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Assessing Quality of Life (QoL) for Individuals with Parkinson's Disease with and without Deep Brain Stimulation: The Development and Preliminary Results of The Parkinson Alliance Quality of Life Scale (PAQLS)

Wertheimer, J .C.[1,2], *Tuchman, M.*[1], *Walton, C.*[1], *Kramer, R.*[1], *Wherry, J.*[1] & *Kingery, L.R.*[1], *Smith, J.*[1, 3]

[1] *The Parkinson Alliance, Kingston, NJ*

[2] *Department of Behavioral Medicine, Brooks Rehabilitation Hospital, Jacksonville, FL*

[3] *Department of Neuropsychology, Henry Ford Hospital, Detroit, MI*

INTRODUCTION: The understanding of how DBS impacts the lives of patients with PD in the context of symptom severity and quality of life continues to be of strong interest. The Parkinson Alliance designed a QoL survey with the intention of creating a unique and comprehensive self-report measure of QoL in PD patients.

METHODS: A mail-survey/questionnaire methodology was used. The participants were recruited from a variety of sources and included a representative sample of PD patients in the United States. The participants included 94 individuals with PD who underwent DBS and a comparison group of 86 individuals with PD without DBS (non-DBS).

RESULTS: Disease duration was significantly different between the two groups; covariate analyses were used to control for differences in the analyses. Individuals with DBS reported fewer symptoms of tremor and dyskinesia, but they reported more symptoms of gait disturbance and poor balance than the comparison group. PD patients with and without DBS reported similar experiences with non-motor symptoms, with exception to speech; DBS patients reported a greater degree of speech-related disturbances. As expected, motor and non-motor symptoms adversely impacted quality of life for participants with and without DBS, and, overall, there was not a statistical difference between the two groups. The DBS specific questions revealed that most participants who had undergone DBS reported satisfaction with the treatment and outcome as it related to DBS therapy. There were only a few treatment/outcome-related variables with which the majority of participants reported dissatisfaction, including distance to travel to meet with a programmer, speech problems, and weight gain. There were many DBS variables that were positively correlated with quality of life for the participants with DBS.

CONCLUSIONS: The PAQLS has proved to be useful in gaining a better understanding of the experience of individuals with Parkinson's disease with and without DBS during this preliminary investigation. In many regards, there were not glaring differences between the two groups, which is an interesting finding since the DBS group had PD almost twice as long as the non-DBS group. This finding suggests that DBS may positively influence quality of life for individuals with a progressive disease that possibly would have been lost without such treatment. Additionally, findings in this study point to specific domains whereon future research can place emphasis.

A Wireless Wearable Controller for an Upper Extremity Neuroprosthesis

Christa Wheeler[1,2] and P. Hunter Peckham, PhD[1,2]
1. Department of Biomedical Engineering, Case Western Reserve University
2. Cleveland FES Center

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 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. 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 for control because it augments the tenodesis grasp and can be implemented bilaterally. 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 designed for command signal acquisition.

The wearable controller includes three gigantic magnetoresistive (GMR) sensors to measure joint angle, the conditioning electronics, and an RF transceiver. A small, dime-sized, magnet is placed on the top of the hand. The GMR sensors are sensitive to small changes in magnetic fields over a wide range and therefore allow accurate position measurements over large variations in gap between the sensor and the magnet. A mechanical joint model with two degrees of freedom was designed for initial evaluation of the GMR sensors. A second mechanical model of a joint with three degrees of freedom was designed for initial evaluation of the controller. Currently, clinical trials are beginning to show the distinct relationship between wrist position and controller output.

Reference

Hart RL, Kilgore KL, Peckham PH. A Comparison Between Control Methods for Implanted FES Hand-Grasp Systems. *IEEE Trans Rehab Eng*, 6(2):208-218, 1998

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New Devices for Deep Brain Stimulation

Todd Whitehurst, Courtney Lane, Jim Makous, and Hugh Larsen

Advanced Bionics Corporation, Valencia CA

Advanced Bionics, a subsidiary of Boston Scientific and the only US manufacturer of cochlear implants, was the first manufacturer to commercialize a rechargeable implantable pulse generator (IPG). The Precision™ spinal cord stimulation (SCS) system received FDA approval in 2004. The device has the smallest mechanical package of any commercially available device and includes the widest range of stimulation parameters (e.g., pulse width up to 1,000 μsec, frequency up to 1,000 Hz). The IPG can support up to two eight-electrode leads, and each of the 16 electrodes has a dedicated, independently controlled current source, allowing precise targeting of the output current. The external charger is a small battery-powered disk that can recharge the IPG within 4 hours, and recharging is typically performed once per week. A remote control with a range of about 60 cm allows the patient to control stimulation and to check the status of the IPG. A tablet PC-based Clinician Programmer is used by a physician to program the IPG.

We are developing the required hardware necessary to adapt the Precision platform to deep brain stimulation (DBS). The size and capability of the Precision IPG will remain the same as described above. The device will likely require recharging approximately once per week for 2-4 hours with typical DBS stimulation parameters, and the IPG is expected to have a total life of approximately 20 years. The electrode lead being produced is similar in size to leads already commercially approved for DBS, but the Precision lead will incorporate 8 electrodes.

Advanced Bionics is also the first manufacturer to produce a microstimulator. The *bion*® microstimulator is a tiny, rechargeable neurostimulator about the size of an electrical fuse (3 mm in diameter and 27 mm long). The *bion*® is currently in clinical trials for pudendal nerve stimulation for the treatment of overactive bladder and for occipital nerve stimulation for the treatment of migraine. A second-generation *bion*® currently under development will be roughly twice the volume of the current device, but will have a longer battery life, requiring recharging once or twice per week for typical DBS parameters. An eight-electrode lead will be attached to this device, allowing it to be implanted on the skull for DBS. This device is also designed to have a wide range of stimulation parameters.

Through a grant from the NIH, we will provide these devices and associated support to researchers for use in animal experiments at no charge. The Precision devices should be available at the end of 2006, and the microstimulator devices at the end of 2007.

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Towards "Molecular Wire" Intracellular Recording: Modeling Interactions of Lipophilic Conductive Polymers with the Phosphoplipid Membrane

Alik S. Widge[1], Maria Kurnikova[2], Xinyan "Tracy" Cui[3], Yoky Matsuoka[1]

1: The Robotics Institute, Carnegie Mellon University, Pittsburgh, PA
2: Department of Chemistry, Carnegie Mellon University, Pittsburgh, PA
3: Department of Bioengineering, University of Pittsburgh, Pittsburgh, PA

Despite continual progress in electrode materials and configurations, development of future generations of neural prostheses will require methods for even more sensitive and specific recording and stimulating of neurons *in vivo*. We have previously demonstrated that conductive polymers from the polythiophene family can be self-assembled into monolayer coatings that improve electrode biocompatibility while lowering impedance. Preliminary experiments in an artificial lipid bilayer system have also indicated that the specific polymer poly(3-(2-ethylhexyl)-thiophene) (EHPT) is lipophilic and able to increase the conductance of a lipid bilayer by an order of magnitude. We have hypothesized that this effect occurs by intercalation of EHPT into the lipid phase of the bilayer, and have proposed that this mechanism could permit intracellular electrical access without causing cell death. Chronic intracellular access would be a substantial step forward in the quest for more effective neuron/electrode communication.

In the current work, we use *in silico* molecular dynamics experiments to verify the hypothesized insertion of EHPT into phospholipid membranes. We have used *ab initio* quantum chemical calculations to parameterize polythiophenes for simulation and verified that the derived parameters produce conformations consistent with other investigators' simulations and experimentally derived structures. Through the use of statistical sampling techniques such as replica exchange, we can efficiently explore the large and rugged potential space of EHPT chains in proximity to a model phospholipid bilayer and assess the feasibility of insertion. We present here the first results of our simulations and discuss the implications of these results for our hypothesized mechanism and for potential future molecular engineering of the system.

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Abstract

Development of a caping process based on Si and LTCC for a wireless neuroprosthetic implant

M. Wilke [1,2], M. Töpper [1,2], S. Kim [2], M. Klein [1], K.-H. Drüe [3], J. Müller [3], M. Wiemer [1], V. Glaw [1], H. Oppermann [1], F. Solzbacher [2], H. Reichl [1]

[1]*Fraunhofer Institute for Reliability and Microintegration IZM, Berlin, Germany*
[2]*Department of Electrical Engineering, University of Utah, SLC, UT*
[3]*Institut für Mikro- und Nanotechnologien, Technical University Ilmenau, Ilmenau, Germany*

A wireless neuroprosthetic implant has been developed to chronically record neural signals from central or peripheral nerves. This neural interface consists of a 10x10 microelectrode array, a 100 channel signal amplifier, data compression, RF communication, power recovery module, two 60-turn planar coils (Au on Polyimide) on a ferrite substrate, and SMD components. The array is a silicon based 3-D structure with tapered Si spikes which have a length of 1.8 mm. The System was assembled by flip chip bonding the IC on the Array and stacking the other components one above the other using AuSn solder for electrical contacts. The precise description of this biocompatible integration concept was already published.

The objective of this work was to develop a new packaging concept for the existing implant to allow simpler and more reliable assembly and encapsulation process. In order to protect the system from humidity, ingression of ions and mechanical impact, a solid shell is developed that covers the most sensible components on the backside of the electrode array. The assembly steps are split up into two main parts. The IC is flip chip bonded and underfilled as done before while the shell is loaded with all passive components. In one solder step both parts are bonded together, which forms a hermetic sealing as well as an electrical interconnection.
Two different SIP technologies using Silicon and Low Temperature Cofired Ceramics as encapsulation material are presented to realize the shell.

1. Silicon is KOH etched in order to obtain tapered side walls on which an electric rewiring can be formed by common photolithography and plating steps. In this case, the main issue is to deposit and expose the photoresist in an approximately 600µm deep cavity. An electrodeposited photoresist is therefore compared with a spray coating process. The adaption of the mask design is evaluated in order to guarantee the resolution of the deeply located structures.
2. The LTCC shell is fabricated by laminating, stencil printing and cofiring of green tape ceramics. The advantage of this solution is that the hull serves as encapsulation as well as ferrite core for the coil and therefore saves space. Furthermore it is easy to realize the electrical rewiring. It is investigated how the thermal mismatch between silicon and LTCC influences the use of this material.

Both variations are investigated especially how they influence the power transmission to the system and therefore how they have to be designed in order to ensure an efficient power supply.

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Evaluation of Head Orientation and Electromyography as Command Interfaces for a Computer Mouse

Matt Williams[1,2] *& Robert Kirsch*[1,2,3]

1) Department of Biomedical Engineering, Case Western Reserve University
2) FES Center of Excellence
3) Louis Stokes Cleveland Department of Veterans Affairs Medical Center

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 care givers. One aspect of this loss is the inability to operate a computer in an efficient manner. In an increasingly computerized world, this deficiency is becoming more significant over time. Despite the considerable loss of many voluntary actions, a number of potential command sources remain by which the user can produce the required control signals necessary to restore computer operation. Two of these command sources are orientation of the head and the electromyogram (EMG) of non-paralyzed muscles which remain under voluntary control. This study is an investigation of these potential command interfaces and their applicability as inputs to reproduce the function of a computer mouse.

While head orientation and EMG input for various applications is a well-developed technology, little quantitative evaluation has been performed. Additionally, the use of cervical EMG to control of a computer mouse is novel in the rehabilitation field. These technologies are attractive as user interfaces as they are easily modulated by a user, able to be obtained using conventional means, and are mature technologies that are either easily wearable or readily implantable or in the final device.

Both healthy and subjects with a spinal cord injury were evaluated. Head orientation was measured using a small, lightweight sensor worn on the head with a head band. The muscles used in the EMG portion of the study were the platysma, the trapezius, and the auricularis or frontalis, depending on the capabilities of the user. EMG signal recordings were collected either through surface electrodes or using implanted electrodes as part of a more complex neuroprosthesis for restoration of hand and arm function in the case of impaired subjects. User signals were sent to a PC via a standard serial port. A custom cursor control evaluation program was used to quantitatively measure the performance of each command interface. A gated ramp algorithm with a floating threshold was used to determine user intent for both interfaces.

Users were able to use the interfaces to move the cursor about the screen in two dimensions to reach randomly presented targets of various sizes. Preliminary results indicate that head orientation is approximately twice as effective for cursor motion compared to EMG signals and was preferred by the users.

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High-Gamma Synchronization During an ECoG-based BCI Cursor Control Task

J. Adam Wilson[1], Elizabeth A. Felton[1], P. Charles Garell[2], Justin C. Williams[1,3]

[1]*Department of Biomedical Engineering, University of Wisconsin – Madison*; [2]Department of Neurosurgery, New York Medical College; [3]Department of Neurological Surgery, University of Wisconsin – Madison Hospital

Many brain-computer interfaces (BCIs) use changes in power in one or more frequency bands during an imagined activity as a control signal for an application, such as moving a computer cursor. It has been shown that increases in gamma (35-45 Hz) power and high-gamma (45+ Hz) power occur during movements when recorded from electrocorticogram (ECoG) [1-2]. Our research shows that high-gamma power increases occur during BCI tasks using motor imagery, and that it may be used as a control signal for a BCI system.

We have tested ten patients with medically intractable epilepsy or chronic de-affernation pain who have been implanted with subdural ECoG implants. The ECoG electrodes used were most commonly an 8x8 grid, with a center-to-center distance of 5 mm, and an exposed diameter of 2.3 mm. ECoG signals contain high frequency content because the electrode grid is implanted subdurally, and thus do not suffer from temporal and spatial blurring as EEG does.

In three subjects, gamma and/or high-gamma frequency bands were selected as control signals for a BCI cursor-control task. These subjects were able to achieve high success rates (> 75% hit-rate) during a cursor-control task. Data was analyzed off-line following testing to measure event-related synchronization (ERS) in high-frequency bands. Increases in high-frequency power immediately preceded the start of the control phase of the cursor task when gamma or high-gamma frequency bands were selected to move the cursor. Little or no gamma or high-gamma synchronization was measured on the selected electrodes if no imagery was used. In addition, on electrodes where alpha or beta frequency bands were selected as control signals, high-gamma synchronization still occurred sporadically during many trials.

High-frequency content and spatial resolution on the mm scale in the ECoG may be able to provide a more direct indication of underlying brain function than low-frequency content can. As a result, ECoG recorded from a subject utilizing multiple imagery modalities could be used as a control signal for BCI applications, resulting in independent control signals on neighboring electrodes and increased degrees-of-freedom for control.

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Topic Area: Brain-Computer Interfaces

Determination of subthalamic nucleus location by quantitative analysis of the "despiked" background neural activity along the microelectrode track for deep brain stimulation surgery

Shabbar F. Danish, Gordon H. Baltuch, Jurg. L. Jaggi, Leif H. Finkel
Brian Litt, and Stephen Wong

Introduction: The subthalamic nucleus (STN) has become the preferred target for deep brain stimulation in cases of medically refractory Parkinson's disease. Microelectrode recording during deep brain stimulation surgery is a useful adjunct for intraoperative localization of the STN. The quantitative analysis of the microelectrode recording rests upon identification of individual neurons and their discharge characteristics. The subsequent characterization of neuronal discharge patterns can be somewhat subjective in nature. We hypothesize that there is distinctive information in the "background noise" which can help identify the location of the subthalamic nucleus. We present a novel algorithm and approach to the quantitative analysis of the background noise along the microelectrode track and its utility in determining the location of the subthalamic nucleus.

Methods: Six microelectrode tracks from six patients were retrospectively analyzed. All signals were digitized and exported to Matlab for further analysis. Spikes were identified via an automated algorithm, and subsequently removed from the signal recording. The remaining "despiked" signal was analyzed in a sliding window paradigm with RMS amplitude and Curve length features, which are sensitive to amplitude and frequency. These features were plotted vs. time and evaluated for recurring patterns. STN entry and exit points were chosen based on a sustained deviation from baseline for each of these features, and compared against those determined intraoperatively by the clinical neurophysiologist.

Results: Spike removal resulted in truncation of the data to 94.8±1.5% of its original length. In STN, the RMS amplitude and Curve length features exhibited a consistent and sustained rise in 5 out of 6 tracks. Mean normalized RMS amplitudes in STN, versus those in the flanking 1mm, were 0.56±0.23 and 0.27±0.24, respectively. Mean normalized Curve length values were 0.58±0.31 and 0.40±0.29, respectively. STN entry point prediction was within 0.5mm accuracy for 3/6 tracks and 4/6 tracks, respectively. 1.0mm accuracy or better was seen in 4/6 tracks and 5/6 tracks, respectively. STN exit point prediction for these features was accurate to within 0.5mm in 2/6 tracks and 4/6 tracks, respectively. 1.0mm accuracy or better was seen in 5/6 tracks using both features.

Conclusions: Information in the despiked background noise can allow accurate identification of STN location along the microelectrode track. A sustained rise in RMS amplitude and Curve length in STN, likely reflecting a general increase in neural activity in the background noise, can be utilized for rapid identification of the STN boundaries. This type of analysis can be especially useful in recording situations when the presence of recording artifacts makes single unit differentiation inaccurate. Algorithms of this type may provide useful adjunctive information while attempting to identify the subthalamic nucleus along the microelectrode track.

Optimizing Stimulation Waveforms for Electrical Excitation of Nerve Fibers

Amorn Wongsarnpigoon, John P. Woock, Paul B. Yoo, Warren M. Grill

Department of Biomedical Engineering, Duke University, Durham, NC

Models and Stimulation Paradigms

When selecting stimulation parameters for implantable electrical stimulators, considerations of efficiency—including energy, charge, and power—are important to extend battery life and minimize tissue damage. Previous studies have proposed that a rising exponential is the energy-optimal waveform for excitation of nerve fibers. However, this conclusion was drawn from a nerve fiber model that did not include accommodation. We measured threshold currents for square, ramp, and rising exponential waveforms both in computational models that included accommodation and in in vivo experiments and calculated energy, charge, and power efficiencies. In the computational model, the square waveform was more energy efficient than the exponential waveform for pulse widths (PW) $\leq$ 0.1 ms. At longer PW the square waveform was less energy efficient than the exponential waveform, but the differences in efficiency were less than previously predicted. Measurements of excitation thresholds of cat sciatic nerve revealed no significant differences in energy efficiency between square and exponential waveforms for PW $\leq$ 0.05 ms; at longer PW the differences in energy efficiency were either not significant or less than previously predicted. Several trends were observed in both the model and experiments. The square wave was the most power efficient waveform shape for all PW, and all waveform shapes were most power efficient at long PW (1 ms to 10 ms). Each waveform shape was more charge efficient at shorter PW than at longer PW; in almost all cases, charge efficiency decreased monotonically as PW increased. For PW $\leq$ 0.05 ms, there were only small differences in charge efficiency among the waveform shapes. All waveform shapes were most energy efficient at intermediate PW (0.1 ms $\leq$ PW $\leq$ 0.5 ms). Our results contradict the claim that exponential waveforms are more energy-efficient than square waveforms for all PW. For all three waveforms, the PW at which energy, charge, and power efficiencies were at a minimum did not coincide, suggesting that stimulation parameters should not be chosen based solely upon one measure of efficiency. Rather, stimulation parameters for

implantable stimulators should be chosen based upon a cost function that reflects the relative importance of energy, charge, and power for a given situation.

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Control of continence and micturition by stimulation of pudendal genital afferents

John P Woock, Paul B Yoo, Warren M Grill

Department of Biomedical Engineering, Duke University, Durham NC, USA

Individuals living with spinal cord injuries may face a number of complications related to urinary function. Our goal is to develop a neuroprosthesis that will allow an individual to regain control of their urinary function and experience a healthier and more able life. Our approach is to stimulate sensory fibers in the pudendal nerve to activate spinal reflexes to control continence and micturition. The purpose of these experiments was to measure the physiological responses evoked by stimulation of the genital branch of the pudendal nerve. In 7 male cats, anesthetized with alpha-chloralose, the bladder responses evoked by electrical stimulation of the dorsal genital branch of the pudendal nerve were studied across a range of frequencies (f=1-40 Hz). Depending on the stimulation frequency, electrical stimulation of the dorsal penile nerve elicited either micturition-like or continence-like bladder responses in 6 of 7 cats. The ability to evoke those responses was also dependent on the bladder volume and the stimulus amplitude. Robust increases in bladder pressure, above both the baseline pressure and the pressure during distension-evoked bladder contractions, were observed for stimulation at 20, 33, or 40 Hz in greater than 80% of the stimulation trials (n=268). Stimulation at 33 Hz elicited greater increases in average bladder pressure ($37\pm10 cmH_20$, n=78) than that at 20 Hz (33 ± 11 cmH_20, $p<0.001$,n=72) or 40 Hz (34 ± 9 cmH_20, $p<0.001$,n=54). The average bladder pressure evoked by stimulation at 33Hz was also greater than the average bladder pressure during distension evoked reflex contractions ($16\pm5 cmH_20$, $p<0.001$, n=33). Stimulation at 5, 7.5, or 10 Hz produced excitation in less than 10% of the stimulation trials (n=123), but effectively inhibited the bladder (characterized by suppression of distension-evoked contractions) when stimulation was initiated during distension-evoked contractions. Stimulation at low frequencies (1 and 2 Hz) elicited responses that were inconsistent across trials and animals. These results demonstrate that activation of pudendal genital afferent nerve fibers evoked frequency-dependent bladder activity consistent with normal continence and micturition reflexes. This suggests that there is potential to develop a neural prosthesis utilizing electrical stimulation of pudendal genital afferent nerve fibers to provide control of urinary function to individuals living with spinal cord injuries.

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A Novel spatial selective stimulation model for functional electric stimulation

Zhi Yang, Wentai Liu

Department of Electrical Engineering, UC Santa Cruz, CA

A high density and localized stimulation is always a great challenge in any neuron prosthesis. In this study, a spatial selective stimulation model (virtual electrode) is presented as a method of increasing the number of focus stimulation areas without increasing the number of physical electrodes. The feasibility analysis is investigated using a stochastic neuron model which is based on the EM theory, the individual ion channel model and the compartment cable theory. A detailed mathematical analysis and simulation have been carried out which show that an increased number of pixels with more localized stimulation can be achieved by carefully designing stimulation pulses and geometry parameters of electrodes.

An E field profile induced from a disk electrode in a tissue environment is simulated using a multiple layer saline-tissue model. Varying both the timing and magnitude of the stimulating current, the external E field and its spatial derivative in both temporal and spatial domains are controllable. Combining the E field distribution with the stochastic neuron model, the induced transmembrane voltage is treated as a continuous Markov process which is able to predict the variations of individual spike's timing and amplitude. The stochastic model provides a flexibility of quantitatively analyzing the focus stimulation area, in which the neurons have the highest possibilities to be activated. By changing the stimulating pulses from different electrodes, the stimulation area moves accordingly hence different pixels are achieved. Additional depressing pulses are used in the model to create a more localized stimulation. In the virtual electrode model, stimulating pulses are designed based on the stochastic neuron model and recordings of both gated-protein current and ionic current in the patch-clamp experiment. Geometry parameters of electrodes must also be carefully chosen to make the virtual electrode model function. Taking retina stimulation as an example, if the distance between electrode array and retina is 30um and electrodes with diameter of 120um, center to center distance between two nearby electrodes should be around 160um.

This model shows the virtual electrode with a ratio of 6:1 is achievable. The maximum current amplitude required to support the virtual electrodes is estimated to be on the order of hundreds of μA. A direct in-vitro validation of the model is being pursued by using MEA. On the other hand, indirect proof of the model can be obtained either by intracellular or extracellular recordings with short pulse electric stimulation.

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High Power Efficiency Coil Design for Biomedical Telemetry

Zhi Yang, Wentai Liu

Department of Electrical Engineering, UC Santa Cruz, CA

Inductively linked coils are commonly used in biomedical telemetry as a method to transmit power and data. The coil needs to be designed to have a high efficiency and data rate. The most important parameter of coil is its quality factor (Q), which is frequency dependent and determined by its equivalent serial resistance (ESR) and effective inductance, both of which are functions of frequency. At radio frequencies the ESR of a coil is significantly higher than the DC resistance mainly due to the skin effect and proximity effect. At the same time the effective inductance is less than the DC inductance because parasitic capacitances between turns and strands reduce the inductance. At the self resonant frequency, the AC inductance and Q are close to zero. The maximum carrier frequency is limited to below this resonant frequency and will therefore limit the maximum data rate. For coils in biomedical telemetry, it is desirable to have high Q at the carrier frequency. Without a careful design, especially in implanted coils where there are strict geometry limitations, a low Q will result in heat dissipation and inefficient power transmission. The problems associated with a low Q at the carrier frequency sometimes even result in an unusable telemetry system. In this study, a closed form solution of Q is proposed. f_{peak}, the frequency at which a coil has the highest quality factor, is derived in terms of design parameters. By varying these design parameters, one can select f_{peak} close to the desired carrier frequency. This results in high Q for the carrier frequency and the power efficiency of the telemetry system will be optimized.

Design examples to illustrate the trade off between design parameters of a coil and its f_{peak} and Q are presented in this study. Simulation shows that f_{peak} can be tuned from tens of KHz to tens of MHz for different target frequencies. Several coils have been wound to validate the proposed theory, and measured results of f_{peak} and Q agree with the predictions. With the methodology presented in this paper one can design coils that hit the target carrier frequency, obtain a high Q, and have a high bandwidth. The analytical solutions provided in this study can be used as a guideline to design high Q coils for biomedical telemetry.

DIFFERENTIAL FREQUENCY TUNING AMONG PUDENDAL AFFERENT PATHWAYS GENERATING REFLEX BLADDER CONTRACTIONS IN CATS

Paul B. Yoo and Warren M. Grill
Department of Biomedical Engineering, Duke University, Durham, NC

Electrical stimulation of the pudendal nerve (PN) can activate a spinal micturition reflex causing bladder contraction and relaxation of the external urethral sphincter. Non-specific electrical stimulation of the compound PN can generate bladder emptying (64% of initial volume) that exceeds the voiding efficiency of both distention-evoked reflex micturition (40%) and electrical stimulation of the sacral nerve roots (25%) in cats. However, this degree of emptying is insufficient for neural prosthetic control of bladder emptying following spinal cord injury. Therefore, we sought to characterize the properties of excitatory reflexes mediated by selective excitation of distinct subsets of pudendal nerve afferents as potential substrates to enhance bladder emptying.

The pudendal nerve and its distal branches were exposed in five adult male cats anesthetized with α-choloralose, and bipolar nerve cuff electrodes were implanted on each branch: urethral sensory (US), deep perineal (DP) and inferior rectal (IR). Twenty-second trains of current pulses were delivered to each branch at varying amplitudes (threshold – 2 mA) and frequencies (2 – 50 Hz); while detrusor pressure and electromyograms of the external anal sphincter (EAS) and external urethral sphincter (EUS) were recorded.

In all five experiments, robust sustained bladder contractions (SBC) were evoked through each PN branch. Electrical stimulation of the DP branch consistently generated reflex bladder responses at higher stimulation frequencies (20 Hz $\leq$ f $\leq$ 50 Hz), but statistical analysis of the percentage of SBC-evoked stimulation trials showed that lower frequencies (2 Hz $\leq$ f $\leq$ 10 Hz; ANOVA, $p = 0.21$) were equally effective. In contrast, both the US and IR branches exhibited greater bladder responsiveness to lower stimulation frequencies (2 Hz $\leq$ f $\leq$ 10 Hz; ANOVA, $p < 0.01$).

The results support the presence of three anatomically different excitatory pathways within the pudendal nerve trunk that respond preferentially to different ranges of stimulus frequencies. Differential stimulation of these pathways may provide a means to enhance the efficiency of bladder emptying achieved by electrical stimulation of the pudendal nerve.

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Stretchable Microelectrode Arrays for Monitoring Posttraumatic Dysfunction of Brain

Zhe Yu[1], Candice Tsay[2], Stéphanie P. Lacour[3], Sigurd Wagner[2], Barclay Morrison III[1]

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

Traumatic brain injury (TBI) is believed to result from rapid deformation of the brain. As the brain deforms, blood vessels, cells, and synapses, can be damaged at the moment of injury. The delayed cellular, inflammatory, or metabolic alterations after injury may also disrupt the function of the brain and cause posttraumatic epilepsy, memory disturbance, loss of consciousness, etc. To understand the mechanisms underlying posttraumatic dysfunction of the brain, we are developing an *in-vitro* TBI research system that can monitor the electrical activity of brain tissue before, during and after deformation. We have built an *in-vitro* TBI model in which brain tissue is cultured on highly stretchable silicone membranes and is injured by precisely controlled, biaxial stretching. We are now developing stretchable microelectrode arrays (SMEAs) to detect the functional changes of the brain tissue in the TBI model. By combining the SMEAs with our existing TBI model, brain tissues can be directly cultured on the SMEAs and injured while activity can be monitored before, during and after injury.

The SMEAs are based on a new technology for fabricating stretchable metallization. Stretchable conductive layers (5nm Cr/ 25nm Au/ 5nm Cr) are electron beam evaporated and patterned directly on elastic substrate of polydimethylsiloxane (PDMS), and were initially encapsulated by lamination with pre-patterned PDMS films. The SMEA impedance (at 1 kHz, in physiological saline) was measured to be less than 800kΩ during stretching of up to 8.5% biaxial strain. To obtain a thin encapsulation layer with small feature sizes, we are developing a new technology for directly coating and patterning an insulation layer of photo-patternable silicone on the PDMS substrate. To test the new electrode and insulation technologies, we have fabricated prototype arrays on carrier substrates of glass coated successively with an underlayer of PDMS, an electrical conductor sandwich of Cr/Au/Cr, and a photopatterned electrical insulation layer of 15μm-thick silicone. When integrated with a microelectrode array system (MCS, Germany), the prototype arrays were able to stimulate hippocampal slice cultures and record the evoked population spikes. In the presence of 50μM bicuculline, evoked bursting activity was detected. The activity was blocked with 1μM TTX and recovered after TTX wash out. These results indicate that the recorded signals were biological in origin instead of artifact or noise. In addition to its use in an *in vitro* TBI model, the new SMEA technology has potential applications to highly compliant and robust brain machine interfaces.

Clinical Trials of Laryngotracheal Closure for the Prevention of Aspiration in Dysphagia

Nina Zobenica[1,2], Michael Broniatowski M.D.[3,4], Jeffrey Huynh[1,2], Dustin J. Tyler Ph.D.[1,2]

1) Dept. of Biomedical Engineering, Case Western Reserve University
2) Cleveland VA Medical Center 3) St. Vincent's Charity Hospital
4) University Hospitals of Cleveland

Swallowing difficulties, or dysphagia, are co-morbidities in 75% of stroke victims. Swallowing involves several mechanisms that protect the airway as food travels down to the esophagus. Laryngeal elevation, vocal cord closure, epiglottal closure and oral control all contribute to the protection of the trachea. These actions are coordinated by circuitry in the cortex and brain stem. This circuitry is often damaged in stroke, resulting in dysphagia. Of the mechanisms to protect the airway, vocal fold closure has been identified as most important. Since the muscles controlling vocal fold adduction are all innervated by the recurrent laryngeal nerve, our hypothesis is that stimulation of the recurrent laryngeal nerve during swallowing will close the cords and prevent aspiration. The feasibility has been previously shown in dogs.

The experimental design is a case study, self-controlled, non-randomized design with 10 subjects who are one year post stroke with chronic aspiration. The subjects are implanted unilaterally with a modified Finetech stimulator and Huntington Medical Research Institute bipolar helical nerve cuff on the recurrent laryngeal nerve. Vocal cord closure with stimulation is verified using a flexible endoscopic view. Modified barium swallow tests are performed with stimulation ON and OFF to observe whether aspiration is occurring. To date, five subjects have been enrolled. In all subjects, vocal cord adduction was seen in response to stimulation. Three subjects have exhibited reduction of aspiration with stimulation. One subject has cricopharyngeal constriction and aspirates. One subject was recently implanted and testing results are not yet available. Our results support the hypothesis that unilateral stimulation of the recurrent laryngeal nerve during swallowing will close the vocal cords and reduce aspiration.

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