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Brain Machine Interfaces

Implications for science, clinical practice and society

Ystad Saltsjöbad, Sweden
August 26th – 29th 2010

Organising committee
Neuronano Research Center, Lund University, Sweden

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- Nils Danielsen
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Sponsors:

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The Swedish Research Council (Vetenskapsrådet)
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Social Events

Welcome Mingel
Those who are arriving before the symposium starts are welcome to join us for a mingle with drinks and snacks in the gallery ("galleriet") of the hotel at 20.00 pm in the evening of August 25th.

Free guided tour of Ystad
Friday 27/8, 16.30 pm, 1.5-2 hours

This tour will show you some of the pearls Ystad has to offer. Mystery hangs heavy in the air when we walk through the narrow, cobblestone streets - the settings for the Kurt Wallender novels. We will see some of the 300 unique half-timbered houses from the 13-15th centuries. Our tour will also show us the medieval highlights, but also some modern houses like the theater which was built 1892.

The tour starts with a bus trip from the hotel at 16.30 pm to Ystad and ends on the same bus back to our hotel. On the bus the guide will introduce us to the history of Skåne, the southern-most province of Sweden. In case of rain, the tour will be a bus trip around the area.

Please notify Andrea Nord if you would like to attend the guided tour. It is also possible to register for this event at the symposium.

Symposium Dinner
Saturday 28/8, 19.00, welcome drink starts at 18.30. The dinner will be followed by a dance from ca 21.00 – 01.00.

Games
26-28/8 afternoons

There are opportunities to play games like kubb or boule at the beach. Find your teammates, go to the reception, borrow what you need and wander off to a nice spot where you can play. If you show up later, a tip is to just join the winning team.

Brain Machine Interfaces –

Implications for science, clinical practice and society

August 26th-29th 2010, Ystad Saltsjöbad, Sweden

PROGRAM

THURSDAY August 26th 2010

07.00 - 08.15		Breakfast
09.30 - 09.45		**Opening of the symposium** – Susanne Iwarsson, Pro-Dean, Medical Faculty, Lund Univeristy Sweden Jens Schouenborg, NRC, Lund University, Sweden
09.45 - 10.15	Brain Machine Interfaces - general	**Philip R. Kennedy**, Neural Signals Inc, Duluth, USA *Making the lifetime connection between brain and machine for restoring and enhancing function*
10.15 - 10.45		**John P. Donoghue**, Brown University, USA *The Human Neural Interface: Restoring Function by Merging Brain and Technology*
10.45 - 11.15		Coffee break
11.15 - 11.45		**Andrea Kübler**, Universität Würzburg, Germany *Brain-Computer Interfaces for communication in locked-in patients*
11.45 - 12.15		**Miguel A.L. Nicolelis**, Duke University, USA *Towards a Whole Body Neuroprosthetic*
12.15 - 12.30		**Discussion** – led by Roland S. Johansson, Umeå University, Sweden
12.30 - 14.00		Lunch
14.00 - 14.30		**Andrew B. Schwartz**, University of Pittsburgh, USA *Useful Signals from Motor Cortex*

14.30 - 15.00	Brain Machine Interfaces - general	**Eberhard E. Fetz**, University of Washington, USA *Applications of implantable recurrent brain-computer interfaces*
15.00 - 15.30		**Jens Schouenborg**, NRC, Lund University, Sweden *Toward ultra thin multichannel electrodes for studies of learning and memory in vivo*
15.30 - 15.45		**Discussion** - led by Hans Hultborn, University of Copenhagen, Denmark
15.45 - 19.00		Coffee break plus free time for visiting exhibits, poster session and free discussion
19.00 - 21.00		Dinner

FRIDAY August 27th 2010

07.00 - 8.30		Breakfast
08.30 - 09.00	Deep Brain Stimulation	**Sten Grillner**, Karolinska Institute, Sweden *The Logics of Networks in Motion - mechanisms for selection and control*
09.00 - 09.30		**Alim-Louis Benabid**, Université Joseph Fourier, France *Deep Brain Stimulation: Brain Machine Interfaces at large, where are we going to?*
09.30 - 10.00		**Jens C.H. Sørensen**, University of Aarhus, Denmark *Development of neuromodulation treatments in a large animal model - Do neurosurgeons dream of electric pigs?*
10.00 - 10.15		**Discussion** - led by Anders Björklund and Angela Cenci-Nilsson, Lund University, Sweden
10.15 - 10.45		Coffee break
10.45 - 11.15		**Joshua D. Berke**, University of Michigan, Ann Arbor, USA *Basal ganglia dynamics during action initiation and suppression*

11.15 - 11.45	Deep Brain Stimulation	**Christelle Baunez**, CNRS, France *A few examples of the contribution of animal research for clinical application of Deep Brain Stimulation*
11.45 - 12.15		**Andres M. Lozano**, University of Toronto, Canada *Deep Brain Stimulation- challenges and opportunities*
12.15 - 12.30		**Discussion** – led by Anders Tingström, Lund University, Sweden
12.30 - 14.00		Lunch
14.00 - 14.30	Auditory and visual prostheses	**Rob Shepherd**, The Bionic Ear Institute, University of Melbourne, Australia *Cochlear and retinal prostheses: an overview of safety and efficacy, neural rescue and brain plasticity studies*
14.30 - 15.00		**Blake Wilson**, Duke University, USA *Cochlear implants: Matching the prosthesis to the brain and facilitating desired plastic changes in brain function*
15.00 - 15.30		**Kevin Otto**, Purdue University and Patrick J. Rousche, University of Illinois at Chicago, USA *Neural microstimulation parameters and interfacial quality effects*
15.30 - 16.00		**Dick Normann**, University of Utah, USA *The Feasibility of a Cortically Based Visual Prosthesis: Stimulation and Recording in Monkey Visual Cortex with Chronically Implanted Microelectrode Arrays.*
16.00 - 16.15		**Discussion** – Måns Magnusson, Skåne University Hospital, Lund, Sweden
16.15 - 19.00		Coffee break plus free time for visiting exhibits, poster session and free discussion
16.30 - 18.30		**Social event - guided tour of Ystad** Bus from hotel at 16.30, return 18.30.
19.00 - 21.00		Dinner

SATURDAY August 28th 2010

07.00 - 8.30		Breakfast
08.30 - 09.00	Biomaterial compatibility	**Lars Magnus Bjursten**, Lund University, Sweden *Physical and chemical factors influencing the biocompatibility of an implant*
09.00 - 09.30		**Patrick Tresco**, University of Utah, USA *A Biologically-based Design Strategy for Reducing the Foreign Body Response to Chronically Implanted Neural Interfaces*
09.30 - 10.00		**Jonas Thelin**, NRC, Lund University, Sweden *Biocompatibility and CNS: need for standardization?*
10.00 - 10.15		**Discussion** - led by Nils Danielsen, NRC, Lund University, Sweden
10.15 - 10.45		Coffee break
10.45 - 11.15	Restoring spinal function	**Serge Rossignol**, Université de Montréal, Canada *Reviving the CPG after spinal cord injury*
11.15 - 11.45		**Gerald E. Loeb**, University of Southern California, USA *What does the brain control?*
11.45 - 12.15		**Dejan B. Popovic**, Aalborg University, Denmark *Advanced use of electrical stimulation for recovery of function*
12.15 - 12.30		**Discussion** - led by Jens Schouenborg, NRC, Lund University, Sweden
12.30 - 14.00		Lunch
14.00 - 14.30		**Vivian Mushahwar**, University of Alberta, Canada *Restoring Standing and Walking by the Reactivation of Central Neural Networks*

14.30 - 15.00	Restoring spinal function	**Andrew Jackson**, Newcastle University, UK *Reanimating the arm and hand with intraspinal stimulation*
15.00 - 15.15		**Discussion** – led by Ole Kiehn, Karolinska Institute, Sweden
15.15 - 15.45	Ethics	**Paul J. Ford**, The Cleveland Clinic Foundation, USA *Ethics of Control and Consent in Brain Stimulation for Parkinson Disease*
15.45 - 16.00		**Discussion** – led by Ulf Görman, NRC, Lund University, Sweden
16.00 - 19.00		Coffee break plus free time for visiting exhibits, poster session and free discussion
19.00 - 21.00		**Symposium Dinner** Welcome drink starts at 18.30, dinner followed by dance ca 21.00 - 01.00

SUNDAY August 29th 2010

07.00 - 8.30		Breakfast
08.30 - 09.00	Analytical tools	**Apostolos P. Georgopoulos**, University of Minnesota, USA *Neuroprosthetics and Neuromarkers*
09.00 - 09.30		**Partha P. Mitra**, Cold Spring Harbor Lab, USA *Neural Signal Processing: At the Interface Between Basic and Clinical Neuroscience*
09.30 - 10.00		**Ad Aertsen**, University of Freiburg, Germany Inference of hand movements from population activity in monkey and human sensorimotor cortex: Towards Brain-Machine Interfaces
10.00 - 10.15		**Discussion** – led by Martin Garwicz, NRC, Lund University, Sweden
10.15 - 10.45		Coffee break

10.45 - 11.15	From in vitro to BMI	**Peter Fromherz**, Max-Planck-Institute for Biochemistry, Germany *Semiconductor Chips with Ion Channels, Nerve Cells and Brain Tissue*
11.15 - 11.45		**Laura Ballerini**, University of Trieste, Italy *Interfacing Neurons with Carbon Nanotubes: (re)engineering single-neuron excitability and network connectivity in Cultured Brain Circuits*
11.45 - 12.15		**Martin Kanje**, Lund University, Sweden *Nanomodified surfaces and neurite outgrowth*
12.15 - 12.30		**Discussion** – led by Martin Kanje, Lund University, Sweden
12.30 - 14.00		Lunch
14.00 - 14.30	Nanotechnology and BMI	**Jonas Tegenfeldt**, Lund University, Sweden *Nanochannels for cell biology and DNA analysis*
14.30 - 15.00		**David C. Martin**, University of Michigan, USA *Establishing Reliable Communication Across the Glial Scar: In-Situ Polymerization of Conjugated Polymers in Living Cortex*
15.00 - 15.30		**Discussion** – led by Lars Samuelson, Lund University, Sweden
15.30 - 15.45		Closing comments - End of symposium
15.45 - 16.00		Coffee

Lecture Abstracts – in alphabetical order

Poster Abstracts – in alphabetical order

Inference of hand movements from population activity in monkey and human sensorimotor cortex: Towards Brain-Machine Interfaces

Ad Aertsen
Neurobiology & Biophysics, Faculty of Biology,
and Bernstein Center Freiburg,
Albert-Ludwig University, Freiburg, Germany

In monkeys, activity of multiple single neurons related to arm movement can be employed to control an external actuator. Based on this work, there is an increasing interest in designing implantable brain-machine interfaces (BMI), enabling real-time control of neuroprosthetic devices. Such movement inference has been demonstrated in humans, but little is yet known about the possibility to decode information for the control of reaching and grasping from different sensorimotor areas activated by hand movements. Evidently, specificity and long-term stability of the recorded signals is essential for successful brain-machine interface applications. Thus, a promising novel approach for robust neurointerfacing is based on neuronal population activity, instead of multiple single neuron activity. Earlier, we demonstrated that local field potentials from monkey primary motor cortex can be as efficient as single neuron activity for decoding arm movements. I will give an overview of these results and present more recent findings, aimed at studying the feasibility of inferring hand movements in humans from population activity measured with electrodes on the cortical surface or even from the scalp.

Acknowledgements
This report summarizes results from ongoing collaborations within and beyond the Bernstein Center Freiburg. Primary research conducted by Carsten Mehring, Jörn Rickert, Tonio Ball and their collaborators. Contributions by and stimulating discussions with many colleagues at BCF and beyond, including Niels Birbaumer, Alexa Riehle and Eilon Vaadia, are gratefully acknowledged. Work supported by the German Federal Ministry of Education and Research (BMBF Grants 01GQ0420 to BCCN, 01GQ0830 to BFNT, and BMBF-GoBio). Further information and publications at www.bcf.uni-freiburg.de and www.bmi.uni-freiburg.de

Interfacing Neurons with Carbon Nanotubes: (re)engineering single-neuron excitability and network connectivity in Cultured Brain Circuits

Laura Ballerini
Life Science Department, University of Trieste, Trieste, Italy

One of the more attractive materials employed to develop nano-bio hybrid systems is represented by carbon nanotubes (CNT). CNT organized fractal-like nano-structure and high electrical conductivity render this material a promising one in the development of neural interfaces. CNT can organize into bundles that mimic neural processes and have been patterned on surfaces for studying the growth and organization of neural networks. Recent work shows that CNT anchored on planar substrates can promote cell attachment, growth, differentiation and long term survival of neurons. Neuron-nanotube interaction depends on CNT purity and on their three dimensional organization. We have shown previously, that the growth of functional hippocampal networks cultured on a conductive CNT meshwork is always accompanied by a significant enhancement in the efficacy of neural signal trans-mission, suggesting that the electrical conductivity of the CNT nano-substrate might be underlying these physiological effects. More recently, we have shown, by single cell electrophysiology, that CNT-substrate direct interactions with neuronal membranes affect single cell activity. Such interactions favor back-propagation of action potentials retrogradely into distal dendrites. To further investigate the influence of CNT scaffolds in the formation and function of cell to cell contacts, we performed simultaneous whole cell recordings from pairs of mono-synaptically coupled neurons. Paired recordings from cultured hippocampal neurons were collected in whole-cell patch clamp, with the presynaptic cell in current clamp mode and the postsynaptic cell in voltage clamp mode. We observed a significant increase in the probability of detecting mono-synaptically coupled neurons when networks are constructed on CNT scaffolds: in control, coupled pairs are 38 % (n=163), while this probability is 58 % (N=133) in the presence of CNT. Since the strength of synaptic transmission can vary during repetitive presynaptic activity, we used the most basic protocol stimulating pairs via a short train of 6 action potentials at a “low” frequency of 20 Hz, which is in the range of spontaneous activity in hippocampal cells. We investigated the short term plasticity behavior of the control and CNT hippocampal synapses, and we found that most control synapses are depressing ones. On the contrary, the responses of CNT synapses are more variable, being, in the large majority of cases not depressing ones, and, occasionally, facilitating ones. Our results propose operatively quite a new way of looking at the properties of hybrid structures consisting of CNT integrated with neuronal circuits, where growth supports are able to instruct construction and modulation of synaptic networks.

Mattson, M.P., et al J. Mol. Neurosci. 14, 175–182 (2000). Hu, H. et al, Nano Lett. 4, 507-511 (2004). Hu, H. et al. J. Phys. Chem. B 109, 4285–4289 (2005). Galvan-Garcia, P. et al. J. Biomater. Sci. Polym. Ed. 18, 1245-1261 (2007). Lovat, V. et al. Nano Lett. 5, 1107–1110 (2005). Mazzatenta, A. et al. J. Neurosci. 27, 6931-6936 (2007). Cellot et al., Nature Nanotechnology vol. 4 pp 126-133 (2009).
Acknowledgments: Financial support from NEURONANO-NMP4-CT-2006-031847

A few examples of the contribution of animal research for clinical application of Deep Brain Stimulation

Christelle Baunez
Lab. Neurobiology of Cognition CNRS UMR6155, Marseille, France

The subthalamic nucleus (STN) is a cerebral structure belonging to the basal ganglia and therefore classically thought as a motor structure. In Parkinson's Disease (PD), a degeneration of dopaminergic neurons, the STN becomes hyperactive. Therefore, reversing this hyperactivity by either lesions or high frequency stimulation (i.e. deep brain stimulation (DBS)) has been proposed as an alternative therapy to the classical dopaminergic treatments. The success of this strategy lead to the fact that the STN is the current target for surgical treatments of PD (Limousin et al., 1995; for review Benabid, 2003). In animal models of PD, we have shown that, although inactivating the STN has beneficial effects in alleviating the motor deficits classically observed in this disease, it can also affect cognitive and motivational functions. In the rat, we have shown that STN lesions or high frequency stimulations impair visual attentional performance (Baunez and Robbins, 1997; Baunez et al., 2007) and increase motivation for food (Baunez et al., 2002). Further investigations regarding the involvement of STN in motivational processes allowed us to show that STN lesion or DBS can reduce motivation for cocaine while increasing motivation for food (Baunez et al., 2005; Rouaud, Lardeux et al., 2010). Since one of the major challenge in the treatment of drug addiction is to diminish the motivation for the drug, without reducing other motivations, it is therefore tempting to suggest that STN DBS could represent a possible strategy for the treatment of cocaine addiction.

Baunez C. and Robbins T.W. (1997) Eur. J. Neurosci., 9: 2086-2099
Baunez C, Amalric M and Robbins TW (2002) J. Neurosci. 22(2): 562-568
Baunez C, Dias C, Cador M, Amalric M (2005) Nature Neuroscience Apr;8(4):484-9
Baunez C, Christakou A, Chudasama Y, Forni C, Robbins TW (2007) Eur. J. Neurosci. 25: 1187-1194
Benabid AL (2003) Curr Opin Neurobiol. 13(6):696-706
Limousin P, Pollak P, Benazzouz A, Hoffmann D, LeBas JF, Broussolle E, Perret JE, Benabid AL (1995) Lancet. 345(8942):91-5.
Rouaud T*, Lardeux S*, Panayotis N, Paleressompoulle D, Cador M, Baunez C (2010) P. Natl. Acad. Sci. USA 107:1196-1200

Deep Brain Stimulation: Brain Machine Interfaces at large, where are we going to?

ALBenabid, C Moro, T Aksenova, NTorres, AVassilyev, TCostecalde, F Sauter, G Charvet, C Mestais,
Clinatec LETI, CEA Grenoble, University Joseph Fourier, CHU, Grenoble France.

Introduction:
Systems featuring an interface between the nervous tissue and devices include stimulators, infusion devices, as well as sensory and motor neuroprostheses aimed at deficit compensation. They all belong to functional neurosurgery. Deep brain stimulators are widely used as therapeutic methods and are in need of innovative evolutions. Various methods for improving mobility of tetraplegics are being designed. Robotized exoskeletons driven by Brain Computer Interfaces (BCI) require the possibility to drive up to 26 degrees of freedom (DoF). Based on nanomicro-technologies, we have undertaken the development of prototypes for new 3D DBS systems or for motor neuroprostheses. For this complex project, all compounds have been designed (implanted electrodes, recording 64 channels of electrocorticogram (ECoG), emission and receiving radiosets, data processing algorithm, motorized limbs), and are being tested. Experiments were performed in rats and primates for proof of concepts, and development of the EEG recognition algorithm.

Methods:
Human:
A programmable multiplexer to connect 5 tetrapolar (20 contacts) electrodes to one IPG (implantable pulse generator) channel has been designed and implanted bilaterally into STN in two Parkinsonian patients. A 50mm diameter titanium implant, telepowered, including a radioset emitting ECoG data recorded by a 64 electrode array using an Application Specific Integrated Circuit (ASIC) is designed to be implanted in a 50mm trephine opening. The antennas (data and power transfer) lay on the skull. Data received by the radioreceiver are processed through an original algorithm (MPLS, CEA patent) using wavelets. Effectors with 1 to 26 DoF can be activated following specific training of subjects. 64-channel cortical stimulators are being derived from this BCI implant prototype.

Rats and Primates:
Animals were implanted with specifically designed electrode sets (17 in rats, 32 in primates) cable-connected to acquisition systems. They had to press a lever to obtain a reward. Online ECoG processing using MPLS allowed detecting the brain signature associated to the lever push (LP). This detection triggers the food dispenser. Location of the electrodes was given by back averaging potentials, and by visual and sensory evoked potentials.

Results:
The 3D multiplexer allowed tailoring the stimulating electrical field to the STN nucleus of the patients. It appears that the multiplication of the contacts affects the life duration of the IPG battery, and suggests elaborating different electrode implantation schemes to achieve an efficient 3D stimulation.

The components of the human implantable cortical BC interface are being tested for reliability and toxicology to meet criteria for chronically implantable medical devices.
The algorithm MPLS has been used in rats and in monkeys. In rats, the signature detection was accurate in about 80% of LPs, false positives could reach 1% of the algorithm decisions, depending on the threshold. The best electrodes are chosen according to the correlation coefficient values as well as to the maximal amplitude of the back averaging potentials. In rats, it appears that they are located over the cerebellar cortex. In monkeys, the larger number of recording electrodes is used to pilot effectors with DoF up to 3.

Conclusions:
Multielectrodes wireless implants are designed to exploit movement related ECoG changes and open the way for BCI ECoG driven effectors, ranging from a computer mouse to a wheel chair and ultimately an exoskeleton for tetraplegic patients. These technologies are also used to develop new generations of Brain Stimulators, either cortical or for deep targets.

Basal ganglia dynamics during action initiation and suppression

Joshua D. Berke
Univeristy of Michigan, Ann Arbor, USA

Deep Brain Stimulation (DBS) is applied to a range of target structures within cortical-basal ganglia circuits, to treat an increasing array of neurological and psychiatric conditions. DBS can have dramatically different behavioral effects depending on the frequency of stimulation. This may reflect both resonant properties of particular neural elements and the interaction between DBS and spontaneous oscillatory activity, among other factors. I will present data from a series of studies in we have explored how basal ganglia oscillations in the beta and gamma range relate to normal behavioral states, how they evolve as animals select and suppress actions, and how they shift frequency following manipulations such as dopaminergic drug administration. We have also been examining the resonant properties of distinct classes of striatal neurons in freely-moving animals, and how fast-spiking interneurons in particular contribute to the dynamic organization of striatal microcircuits. Together, these studies may allow increased understanding of how Deep Brain Stimulation in striatum and elsewhere is able to have frequency-dependent effects on behavioral output.

Physical and chemical factors influencing the biocompatibility of an implant

Lars M. Bjursten
Neuronano Research Center (NRC), Lund University, Sweden

A local inflammatory reaction typically occurs locally for most implanted biomaterials, resulting in capsule formation, a chronic inflammation and an unwanted growth of fibrotic tissue.

Many studies of the mechanisms by which biomaterials trigger capsule formation have been focused on the fundamental interactions between the outermost surface layer of the material and various biomolecules, with perceived importance for the overall biological response to the implanted material. These reports have in general pointed to large differences in the interactions, depending on the investigated model surfaces and the studied biomolecules. In many cases these differences have also been demonstrated to carry over to in vitro cell culture experiments. Along these lines, one strategy has been to minimize the host response by producing surfaces that are chemically inert. An example of this biomaterial selection is the choice of silicon elastomer for breast implants, which exhibits minimal cell toxicity in vitro but elicits a strong foreign body reaction in vivo.

A conflicting observation is that several in vivo studies report that rough implants exhibit better bone integration or less adverse soft tissue response than smooth implants of the same material. The question is where the fundamental difference is between the in vivo and the in vitro situation. I propose that the difference is in the mechanics of the biomaterial – tissue interface. Thus A) mechanical factors have been shown to induce marked different signaling changes in endothelial cells and a variety of other cell types, including macrophages. B) There is ample evidence in the literature to indicate that relative movement of especially bone anchored implants with respect to the surrounding tissue results in a reaction to the implant, followed by its subsequent rejection. C) We have shown that cells (macrophages) at the inert biomaterial–tissue interface undergo necrosis and may contribute to developing the signals required for the foreign body formation at 'inert' implanted biomaterials. Further, activation of the interfacial cells by mechanical shear without causing actual cell death is probably also as important.
It has thus become increasingly more accepted that the mechanical normal and shear stress of the tissue–implant interface determines the magnitude of the response in both bone and soft tissues. This hypothesis may actually explain why surface texture and implant location affect the magnitude of the foreign body response to an implant.

The Human Neural Interface: Restoring Function by Merging Brain and Technology

John P. Donoghue
2Rehabil. Res. and Develop. Service Providence VA Medical Center and Insitute for Brain Science, Brown University, USA

The BrainGate2 neural interface system is a BMI being designed to restore independence, communication and control for people with paralysis. The goal of this system is to allow paralyzed humans to use cortical signals to operate external devices ranging from computer software to robotic assistants to muscles. The system, being developed by our group at Brown University and Massachusetts General Hospital, is now in pilot clinical trials for humans with tetraplegia from spinal cord injury, stroke, or ALS. Control signals are derived from the neural activity in arm area of motor cortex through a small chronically implanted, 100 microelectrode array that enables recordings of action potentials of many neurons as well as local field potentials. Signals from the sensor are decoded externally into a control signal that is operated by user intention. Preliminary BrainGate experience from four tetraplegic participants demonstrate that arm-related motor cortical signals remain in motor cortex years injury, stroke or onset of ALS. System use requires no learning, only creation of a mapping between imagined action and cursor motion, and has low attentional demands, as seen when controlling a computer cursor to reach screen targets. Neural signals are evident more than four and one half years after array implantation, suggesting that such interfaces can be well tolerated for long periods in human cortex. Using BrainGate, participants have operated various assistive devices, including point and click actions of a computer cursor to type and a multijoint robotic arm to grasp objects. Next-step advances toward wireless, fully implanted microsystems and more automated and portable systems are underway by our group. The potential to connect neural signals to implanted functional electrical stimulators could provide a physical means to reanimate paralyzed muscles with natural, volitional signals from cerebral motor areas. Beyond its use in paralysis, direct access to high resolution signals may open up new approaches to monitor brain state acutely or for long term applications. Thus, neural interfaces now promise to provide a new spectrum of approaches to evaluate and treat nervous system disorders and to restore lost functions.

Biocompatibility and CNS: need for standardization?

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Neural interfaces hold great promise to become invaluable clinical and diagnostic tools in the near future. However, the biocompatibility and the long-term stability of the implanted interfaces are far from optimized. It is well known that the implantation procedure is associated with a certain amount of local tissue damage and the implant itself subsequently elicits both acute and chronic reactions in the surrounding tissue. There are several factors that need to be addressed and standardized when improving the long-term success of an implanted electrode. We have chosen to focus on three key factors when evaluating the evoked tissue responses after electrode implantation into the brain: implant size; fixation mode and evaluation period. Especially the issue of combining size and fixation modes is of interest. In a present study we have used quantitative immunohistochemical methods to compare the tissue reactions between 50 µm and 200 µm diameter implants either tethered or un-tethered to the skull focussing especially on the zone with a 50 µm radius from the implant-tissue border using an evaluation period of 12 weeks which is longer than commonly used. This 50 µm distance is of neurophysiological relevance since distances over which spiking activity of individual neurons can be followed rarely exceeds 50 µm. In order to avoid the problem of inserting un-tethered electrodes by hand and tethered electrodes by the aid of a micro-manipulator, which has been the case in previous studies, we have developed an insertion method that can be used for both tethered and un-tethered implants using a micro-manipulator. We deliberately chose to use round implants to avoid the tissue reactions related to sharp edges and corners and thereby also avoiding the problem of compensating for the corners when calculating neuronal density.

Therefore, to improve biocompatibility of implanted electrodes we would like to suggest that free-floating, very small, flexible and, in time, wireless electrodes would elicit a diminished cell encapsulation. We would also like to suggest standardized methods for both the electrode design, the electrode implantation method and the analyses of cell reactions after implantation into the CNS in order to improve the long-term success of implanted neural interfaces.

Applications of Recurrent Brain-computer Interfaces

Eberhard Fetz, Andrew Jackson, Chet Moritz, Yukio Nishimura, Timothy Lucas and Steve Perlmutter (University of Washington)

We are investigating the consequences of artificial connections produced by an autonomous recurrent brain-computer interface [R-BCI] that operates continuously during free behavior and generates activity-dependent stimulation of the brain or muscles. This so-called "Neurochip" consists of battery-powered electronics connected to electrodes that record the activity of motor cortex cells and/or muscles. The neural activity is processed by a programmable computer chip and can be converted in real-time to activity-contingent electrical stimuli delivered to nervous system sites or muscles (Mavoori et al, J. Neurosci. Meth. 148: 71, 2005). A promising application is to bridge impaired biological connections, as demonstrated for cortically controlled electrical stimulation of paralyzed forearm muscles. A recent study (Moritz et al, Nature 456: 639 – 642, 2008) showed that learning volitional control of the relevant neural activity is a promising alternative to the traditional decoding of neural populations for BCI control. A second application of the R-BCI is to produce Hebbian synaptic plasticity through spike-triggered stimulation, which can strengthen physiological connections (Jackson et al, Nature, 444: 56-60, 2006). Recent work has shown that similar plastic changes can be produced by EMG-triggered cortical stimulation and in corticospinal connections by cortically triggered intraspinal stimulation. The R-BCI paradigm has numerous potential applications, depending on the input signals, the computed transform and the output targets.

Support: NIH, Christopher and Dana Reeve Foundation, LSDF, ITHS, AHA.

Ethics of Control and Consent in Brain Stimulation for Parkinson Disease

Paul J. Ford
The Cleveland Clinic Foundation, USA

This presentation will develop and explore ethical issues of control in machine brain interface by discussing our experiences in conducting a mixed methodology study of patients undergoing Deep Brain Stimulation for Parkinson Disease. Many historical and fictional accounts have promulgated fears that brain machine interfaces necessarily impede a person's liberty and autonomy, particularly with respect to control. However, these stories offer only simple imaginative explorations that fail to engage in serious and important ethical challenges of control in contemporary medicine and clinical research.

Academic considerations of control have periodically emerged during the last century related to brain interventions. In particular, control of individuals was hotly debated in the middle part of the 20th century with respect to destructive psychiatric surgeries. At the same time that the debate about destructive psychiatric surgeries occurred, very basic brain implants were being tested for various diseases and behaviors ranging from epilepsy to uncontrollable violence. Researchers like Jose Delgado and Robert Heath prompted great debate regarding the control of minds given their various (in)famous neuromodulation cases. Delgado went so far as to write a book entitled "Physical Control of the Mind: Toward a Psychocivilized Society" (Delgado 1971). More recently we have a Dutch case reported in which a patient with Deep Brain Stimulation having to choose between good motor benefit but with an unanticipated side-effect of psychosis or debilitating motor symptoms and no psychosis (Leentjens 2004). Although discussions and cases have broadly identified issues of control in brain machine interfaces, the challenges have remained only tangentially discussed in the literature with no data-driven investigations from a patient or research participant perspective.

Our current study examines values related to control using DBS for Parkinson disease as a paradigm case and tracks participants pre-implantation values through 6 month follow up. The data is both quantitative and qualitative in nature in order to capture the richness of individuals lived experiences. Understanding how to best respect patients' values of control and to match goals of clinical research to appropriate understandings of control will lead to the development of the most ethically robust policy, research methods, and clinical application for emerging brain machine technologies.

Semiconductor Chips with Ion Channels, Nerve Cells and Brain Tissue

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The physical processes are studied that determine the electrical interfacing between the elementary components of brain and computer. One goal is to develop hybrid systems that allow the study of information processing in neuronal networks. Another aim is to provide a reliable basis for the improvement of neuroprosthetic devices. Care is taken that electrochemical reactions are excluded in order to avoid any damage of hard and soft matter. The following issues are considered in this lecture: (i) The nature of cell/chip and tissue/chip coupling is addressed with core-coat conductor models. (ii) The structure of capacitors and transistors is described with simple silicon chips as well as with multi-site CMOS chips. (iii) The structure of cell/chip and tissue/chip contacts is optically investigated on a nanometer and micrometer scale by fluorescence interference and 2-photon microscopy. (iv) The electrical resistance of cell-chip contacts is probed by AC voltage transfer, thermal voltage noise and voltage-sensitive dyes. (v) The mechanism of capacitor stimulation and transistor recording is elucidated with recombinant Na and K channels. (vi) Capacitor stimulation and transistor recording are characterized with nerve cells from snail and rat. (vii) Simple neuroelectronic hybrids are implemented with two-way silicon chips and two-way CMOS chips. (viii) Rabbit retinae are attached to CMOS chips for capacitor stimulation and transistor recording. (ix) Cultured and acute brain slices from rat hippocampus are interfaced with silicon chips. Their dynamics is visualized at a high spatial resolution with CMOS chips. (x) Capacitors and transistors are fabricated on needle chips and tested in brain tissue and in rat.

Neuroprosthetics and Neuromarkers

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Brain signals can be used for two very different applications, namely neuropros-thetics and neuromarkers. In the former case, they are used to control prosthetic devices or, more generally, to communicate directly with the external world, whereas in the latter case they are used as indicators of brain disease. However different these application may seem, they both use the same kind of information, namely the time-varying, ongoing, electromagnetic signals stemming from synaptic and/or spike activity, and their interactions. In this lecture, I will probe the similarities and differences in the processing and use of brain signals in these applications, with an emphasis on a unified information-processing approach to this problem.

The Logics of networks in Motion – mechanisms for selection and control

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Goal directed locomotion requires not only the generation of the standard motor pattern produced by the CPG networks that are turned on from the brainstem command regions (MLR/DLR), but also a maintained control of body orientation (posture) during the locomotor movements and the control of steering. My presentation, based on the lamprey CNS, will address the intrinsic function of the CPG and particularly the intersegmental coordination (forward-backward locomotion) and its supraspinal regulation. In addition, I will discuss the tectal mechanisms underlying steering movements with the retinotopic motor map, and the control from the output of the lamprey basal ganglia. Furthermore, the mechanism by which different motor programs are selected will be considered with special reference to the basal ganglia – experiments and modelling. Our recent findings establish that the structure and function of the basal ganglia have been conserved to a surprising degree from the ancient lamprey version (around 525 million years) to mammals that appeared much later (around 130 million years). This applies to the input to striatum (pallium, thalamus, dopamine, 5-HT, histamine input), the pallidal structures and their output targets, the cellular properties of striatal and pallidal neurons and the effects of an MPTP induced dopamine denervation.

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Reanimating the arm and hand with intraspinal stimulation

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Despite recent advances in Brain-Machine Interfaces that use neural signals for control of external devices, reanimating the paralysed upper-limb remains a formidable challenge. In humans, 34 muscles act synergistically on the fingers and thumb to produce an enormous repertoire of manipulative ability. In addition, bimanual movements involve intricate co-ordination between limbs. We are exploring electrical stimulation of the cervical spinal cord as a method of activating multiple upper-limb muscles in a co-ordinated manner to restore functional movements of the arm and hand. In this talk I will describe a series of experiments performed in sedated macaque monkeys aimed at elucidating and exploiting motor circuits in the cervical enlargement. Beginning with simple stimulation protocols we develop descriptive models of non-linear spinal input-output relationships that can be inverted to generate complex stimulus trains for naturalistic movements such as reach-and-grasp.

I will present data showing that intraspinal microstimulation recruits motoneurons through a distributed network of connections that span multiple segments and cross the midline, questioning modular models of spinal cord organisation. The variety of spatio-temporal interactions between stimuli delivered at separate cervical sites may increase the range of movements that can be produced from a small number of electrodes, allowing intraspinal microstimulation to span a high-dimensional control space.

Next-generation autonomous implants using appropriate cortical populations to control stimulation patterns may provide an effective neural prosthesis to replace or augment damaged cortico-spinal connectivity and restore upper-limb function to paralysed patients.

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Nanomodified surfaces and neurite outgrowth

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Cells respond to both topographical and chemical cues in their environment. Such cues help to guide nerve cell processes, neurites, to their proper targets during development and regeneration. The guiding properties of micrometer sized structures on cells and neural growth cone is well established. Less is known about the importance of nanosized topographies on cells. Others and we have found that regenerating nerve cell process respond to nanostructures. This could be utilised to guide neurites to the recording and stimulating devices on multi-electrode array chips. Here I will review our attempts to guide neurite outgrowth from organ cultured mouse dorsal root ganglia. The first attempts included porous silicone surfaces (1). These surfaces were found to guide neurite outgrowth dependent on pore size. Lithographic printing of nano-patterns composed of parallel ridges and grooves acted as efficient guides for small calibre neurites which preferentially grew on the ridge edges (2). The most efficient guidance was observed on surfaces endowed with nanowires(3). Arrow-shaped patterns of wires could also be used to separate neurite outgrowth from different ganglia (4). Finally nano-patterns obtained by making casts of basal lamina acted as guides for neurite outgrowth. We conclude that fairly simple topographical nano-sized patterns can be used to guide neurite outgrowth on a chip surface.

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Making the lifetime connection between brain and machine for restoring and enhancing function

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This meeting is concerned with building neural prosthetics and the application of that technology to enhance human brain function. An essential component of any such system is that the connection between brain and machine has to remain stable for the lifetime of the recipient of the brain implant.

This presentation will deal with one solution to forming a stable connection between brain and machine. The principle of growing neuropil into the electrode, rather than poking a sharp electrode tine into the neuropil, is the key to longevity of the recordings. The Neurotrophic Electrode (NE) has been shown to provide a stable signal over many years. In our efforts to develop a speech prosthetic, the NE continues to record useful signals five years after implantation. This electrode consists of a hollow glass cone in which Teflon insulated gold wires are fixed, with neurites being enticed into the tip using trophic factors. The neural signals thus recorded have been used in earlier studies to provide communication between subject and computer programs for assistive communication, and in a more recent speech study the subject was able to produce vowel phonemes with 80% accuracy. Both standard and innovative decoding methods are important to these achievements.

Though it will be many years before neural prosthetics are clinical tools, it will not be too long after that before these technologies become consumer products that enhance brain function. These products will be used to receive and transmit information, enhance memory directly or via cloud computing, and perform higher order calculations. These future products, however, will be less concerned with implementing the technology, but more concerned with understanding which brain pathways will provide access and how the brain will process such large loads of information. Hence, basic neuroscience knowledge is a further key to these developments.

Brain-computer interfaces for communication in locked-in patients

Andrea Kübler

A great effort is undertaken to provide patients in the locked-in state (LIS) and complete locked-in state (CLIS) who have only residual or no muscular activity for communication and interaction with their environment, with a muscle independent means of communication. Brain-computer interfaces (BCI) may constitute such devices. For use in daily life functionality, easiness of use and possibility of independent use are the most important aspects. Several applications for social interaction and entertainment are currently being evaluated by users, such as internet browser, games or brain painting. Different components of the EEG are used for BCI control such as slow cortical potentials (SCP) or sensorimotor rhythms (SMR). Within a neurofeedback training subjects learn to regulate the time course or power of the specific signal. Such regulation requires an intact circuit in which the basal ganglia, thalamus, motor and prefrontal cortical areas are selectively activated and inhibited. Depending on the disease one or more of these areas may be affected rendering BCI control a challenge, and indeed usually patients with motor impairment perform worse in BCI paradigms as compared healthy volunteers. While it was shown in many studies that patients in all stages of motor impairment, even in the locked-in state, are able to communicate via BCI, it remains unclear whether BCIs are feasible for patients in the CLIS; in those patients even with implantable electrodes BCIs have not yet been successful. We may speculate that after a longer period of time in the CLIS intentional behaviour is extinguished due to a loss of contingency between intention and consequences. Nevertheless, in such non-responsive patients a proper diagnosis is of utmost importance to determine cognitive function, consciousness and the ability to communicate. While passive reaction to stimulation can provide us with information the level of cognition only active paradigms including BCI in which individuals have to follow instructions can provide us with information about consciousness. Taken together, BCI allow for the detection of consciousness in non-responsive patients, the control of various applications and whether they also constitute the key for communication in the CLIS remains an empirical question.

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What Does the Brain Control?

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Attempts to use signals from the brain to control prosthetic devices usually start with a guess about what parameters of movement or muscle activity the brain might be encoding, followed by tuning a linear network to convert the available neural activity to those parameters as inputs to the prosthetic controller. Research in monkeys indicates that modest correlations can be found between at least some of the neural activity and any reasonable set of parameters, and that subjects can learn to generate arbitrary neural activity patterns to control an unrelated movement parameter. So why is the performance of BMIs so poor on even simple tasks such as pointing to objects without mechanical interactions? We hypothesize that the problem is the unrealistic design of the whole scheme. Rather than controlling motor behavior explicitly, the brain normally acts indirectly by programming powerful intermediary systems that mix descending command signals with sensory feedback. One such system is the spinal cord, whose circuitry is relatively well-described and which is capable of generating autonomously the complex and adaptive patterns of muscle coordination required for tasks such as locomotion. We have modeled limb subsystems (2 degree-of-freedom wrist and planar elbow-shoulder) equipped with multiple realistic muscles, tendons, proprioceptors and classical spinal interneuronal circuitry for synergistic and antagonistic relationships. A very simplistic model of the supraspinal controller produces background "SET" and step-function "GO" signals that specify the biases of the interneurons, fusimotor drive, and feedback gains of afferent and efference-copy signals, but with NO direct input to the alpha motoneurons. Using only gradient descent adjustment of these control signals, such model systems converge very rapidly on accurate, human-like performance of a wide range of previously studied behaviors, including resisting perturbing torque pulses, rapid changes in posture, rapid isometric torque generation and reaching in the presence of a viscous curl-field. Importantly, when started in various random states, the models converge consistently to good performance but usually via different combinations of gains (Raphael et al., in press). This suggests that the spinal cord circuitry embodies a large number of desirable, stable and easily discovered local minima that can provide rapid solutions to new motor control problems, rather than the globally optimal solution that is prized in engineered systems. Models of the spinal regulator and of muscle mechanics are complex (with hundreds of control points) but they have emergent properties that appear to simplify and accelerate learning to produce complex movements. That alone would provide a basis for their evolution and retention. Designers of neural prosthetic systems intended to perform similar motor tasks will probably need to emulate at least some aspects of these modeled systems. Exactly what aspects will suffice for which tasks remains to be determined.

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Deep Brain Stimulation - challenges and opportunities

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Deep brain stimulation is one of the most important therapies in functional neurosurgery to date. In addition to its established role for the treatment of movement disorders, promising results have now been reported in epilepsy and in psychiatric diseases. The adjustability, reversibility and low profile of side effects of this therapy have made it an attractive alternative to conventional surgery which involved lesioning dysfunctional targets. As a consequence of these advantages, new applications are currently being proposed for diseases previously considered outside the realm of neurosurgery. This presentation will focus on areas of current and future investigation of DBS and cortical surface stimulation and recording including potential uses as a component of brain-machine interfaces.

Establishing Reliable Communication Across the Glial Scar: In-Situ Polymerization of Conjugated Polymers in Living Cortex

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Directly implanted microelectrodes have long been considered for establishing intimate communication with and stimulation of neurons in the cortex. However even after many years of investigations these devices still have serious issues with their sensitivity, reliability, and long-term performance. Histological studies have revealed the persistent formation of a glial scar around the electrode, associated with layers of microglia and activated glia most proximal to the electode surface, as well as the loss of functional neurons. The characteristic width of this scar is approximately 150 microns, or about three cell layers.

Our group has developed methods for the deposition of conducting polymers such as poly(3,4-ethylenedioxythiophene) (PEDOT) on the surfaces of cortical electrodes. These materials can significantly lower the impedance of the device, making it possible increase sensitivity, charge transport, and locally deliver drugs such as neurotrophins and anti-inflammatory agents.

Most recently we have been developing methods for the in-situ polymerization of conjugated polymers in living cortex. The EDOT monomer is delivered locally with a microcannula, and the polymerization proceeds by electrochemical oxidation from the metallic anode. The long-term goal is to create a path for charge transport across the glial scar, ultimately resulting in a stable, intimately integrated device. The potential ability to establish and maintain electrical contact with the surrounding parenchyma also has important implications for other bionic devices including cochlear implants, retinal implants, deep brain stimulators, and pacemakers.

Neural Signal Processing: At the Interface Between Basic and Clinical Neuroscience

Partha P. Mitra
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Electrical activity in neural circuits forms the basis of brain function. Direct measurements of this activity using intra/extracellular electrodes, EEG, MEG, indirect measurements using fMRI or other methods, produce multivariate neural signals or time series. In recent decades, significant progress has been made in understanding and quantifying the content of these neural time series using signal processing methods. These methods have found usage in studying sensory and motor electrophysiology, and has also helped quantify neural dynamics associated with higher order cognitive processes including working memory and selective attention. These applications in basic neuroscience are complemented by clinically motivated applications, such as readouts of intended movements or volitional activity in Brain Computer Interfaces. Signal processing techniques are also important for Brain Stimulation based therapeutic developments, since they provide the possibility of measurement based control. The talk will contain a theoretical overview of neural signal processing methods along with some examples of usage.

Restoring Standing and Walking by the Reactivation of Central Neural Networks

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Loss of standing and walking is a devastating side effect of neural injuries including spinal cord injury, head trauma, and stroke. In this talk, I will summarize our lab's efforts at restoring functional standing and walking capacity through the use of a miniature intraspinal neuroprosthetic interface. I will describe pertinent anatomical features of the spinal cord (in comparison to cortical regions of the brain), long-term performance of microwires interfacing with spinal cord tissue, models of locomotor function, and software and hardware implementations of models of locomotion. I will particularly focus on important features of the neuronal locomotor circuitry and show results from in vivo experimentation demonstrating the effectiveness of the intraspinal neuroprosthetic interface in producing robust overground walking.

This work is supported by the National Institute of Health, the Canadian Institutes of Health Research, the International Spinal Research Fund and the Alberta Heritage Foundation for Medical Research.

The Feasibility of a Cortically Based Visual Prosthesis: Stimulation and Recording in Monkey Visual Cortex with Chronically Implanted Microelectrode Arrays

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We are investigating the use electrical stimulation via microelectrode arrays inserted into the primary visual cortex as a means to restore limited vision to those with profound blindness. We have implanted arrays of penetrating microelectrodes into the cortexes of felines and macaques, and measured the array's electrical parameters, the retinotopic organization of both cat and monkey visual cortexes, and the magnitude of the threshold currents required to evoke behavioral responses in the monkey.

Utah Electrode Arrays containing 96-microelectrodes were chronically implanted into the visual and motor cortexes of monkeys and cats, respectively, as well as acutely in cat visual cortex. Computer generated visual stimuli were presented in acutely implanted cats and chronically implanted monkeys on a computer monitor in a darkened room. Electrical stimuli consisting of 200 ms bipolar trains of 200 Hz (0.2ms pulses) were also delivered to monkey visual cortex. Single-unit action potentials, multi-units, local field potentials, and electrical parameters were recorded in all experiments.

Electrode impedances in chronically implanted cats initially increased post-implantation and then gradually decreased to values around those measured at time of implantation. Retinotopic organization measured in acutely implanted cats was non-conformally related to electrode locations (the difference between receptive field locations and locations predicted by conformal transformation of electrode positions had a standard deviation of around 0.5 degrees of visual angle). This poor retinotopic organization was also observed in preliminary maps made in chronically implanted monkeys. Psychometric 'frequency of seeing' curves for photic stimuli in the monkeys were similar in shape to those measured for human observers, but were -2 log units less sensitive. Psychometric curves for electrical stimulation were similar in shape to those measured for photic stimulation, and had a mean threshold (50% detection) of 30.5 microamps.

These studies support the concept that electrical stimulation of visual cortex with arrays of penetrating microelectrodes evoke phosphenes that could form the basis of a visual prosthesis. The observed changes in electrode impedance, however, indicate that the cortical tissues are reacting to the implanted electrodes over time, an issue that will need to be addressed in future work. Further, the demonstrated non-retinotopic organization of visual cortex may require preprocessing of spatial stimulation patterns in order to evoke percepts with simple geometric shapes.

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Neural microstimulation parameters and interfacial quality effects

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There is a fundamental obstacle to the design of penetrating microstimulation for neuroprostheses. That obstacle is the tissue response to the device insertion and the application of the electrical stimulation. Our long-term goal is to develop multi-channel microstimulation of central nervous tissue for clinical therapy. The overall objective of the proposed research is to identify the optimal stimulation parameters for a chronically-implanted microstimulation device. In particular, our objective focuses on the effects of repeated stimulation and the reactive tissue response on the efficacy of stimulation-driven behavior. Our central framework is that multi-channel microstimulation will be a more effective treatment than low-channel count macrostimulation. We are pursuing two simultaneous experiments: first we are studying how different microstimulation parameters affect the psycho-physical threshold and the dynamic range for sensation. To this end, psychophys-ical experiments are being performed using multi-channel cortical implants in the auditory cortex of rats. Second, we are investigating the effect of the device-tissue interfacial quality on the psychophysical threshold. Chronic implantation of neural implants is followed by a reactive tissue response that both functionally isolates the electrode from the tissue as well as triggers neuronal apoptosis and migration. We measure these functional changes and determine their role in reducing the efficacy of a cortical auditory prosthesis. Here we report the effects of cortical depth, days post-implant, electrode-tissue impedance, and waveform asymmetry on the psychophysical threshold of auditory cortical microstimulation. We expect that these data will further enable neuroprosthetic development for many potential applications of microstimulation.

Advanced use of electrical stimulation for recovery of function

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Electrical stimulation can restore some motor functions in individuals with spinal cord and brain injuries/diseases. The application of the electrical stimulation systems need to be well defined: assistive system (orthosis) or therapeutic modality. However, in both cases the bottleneck for the successful application is insufficient selectivity, difficulty in inhibiting the involuntary activation of sensory-motor systems, and timely activation of paralyzed muscles. The solution for selective stimulation follows the concepts of multiple activation points (multi-pas surface electrodes, distributed stimulators, multi-contact neural electrodes). The inhibition of involuntary activation could eventually be resolved by better activ-ation of sensory systems within the spinal and supra spinal mechanisms. The control that possibly can provide timely activation relies on heuristic modeling of the process. The lecture will also address new interfaces that could improve the operation by integrating cognitive vision and advanced processing of biosignals.

Reviving the CPG after spinal cord injury

Serge Rossignol, M. Martinez, G. Barrière, A. Frigon, O. Alluin, J. Cohen-Adad, H. Delivet-Mongrain, H. Leblond.

Canada Research Chair on the Spinal Cord, Multidisciplinary Teanm on Locomotor Rehabilitation after Spinal Cord Lesion (CIHR) and Groupe de recherche sur le système nerveux central (GRSNC), Department of Physiology, Faculty of Medicine, Université de Montréal

Hindlimb locomotion is a complex motor act involving several control levels of the Central Nervous System (CNS). In the spinal cord, specialized circuitry called the central pattern generator (CPG) generates the basic locomotor pattern. Previous experiments have shown that cats with a complete spinal section at the last thoracic segment (T13) can recover hindlimb locomotion on a treadmill after a few weeks of training. The key role played by the CPG in this condition is thus inescapable. However, is the spinal CPG also involved in the re-expression of locomotion after partial SCI? In this latter condition, numerous changes occur within the CNS. To develop targeted rehabilitation strategies (such as in BMI), it is important to know which of these structures are modified and could be stimulated. The dual spinal lesion paradigm allows the study of changes within the spinal cord itself and how they could contribute to the recovery of hindlimb locomotion. A first partial lesion is performed at T10-11 on one side (assessed by MRI) and then cats are trained or not to walk on a treadmill for several weeks (minimum 3 weeks). After this, the spinal cord is completely transected at T13 and locomotor and reflex capabilities are evaluated as early as 24 hours after spinalization.

During the period between the two spinal lesions, asymmetries in locomotor kinematics and reflexes were clearly observed in the left and right hindlimbs. Moreover, following the partial SCI some cats maintained a 1:1 coupling between both girdles whereas, in others, the fore- and hindlimbs walked at two different frequencies. After complete spinalization, the majority of cats expressed hindlimb locomotion within 24 hours which is normally observed after of 2-3 weeks of training without the initial partial SCI. This indicates major plasticity in the spinal cord following the incomplete SCI. Furthermore, asymmetries in kinematics or in cutaneous reflexes seen after the partial lesion were either abolished or completely reversed after spinalization. In conclusion changes within the spinal cord are important for the recovery of locomotion not only after complete section but also after an incomplete SCI. We are currently evaluating the importance of locomotor training in the latter condition.

These observations in animals (similar observations are emerging in rats) highlight the importance of spinal mechanisms in the recovery of function. This may be questioned for SCI in humans since the notion of a spinal CPG is not widely accepted. However, mounting evidence also suggests the existence of endogenous rhythmogenic circuits in humans, which could therefore be targeted in rehabilitation strategies after SCI.

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Toward ultra thin multichannel electrodes for studies of learning and memory in vivo

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The Neuronano Research Center (NRC) is a cross disciplinary research center, consisting of researchers from the faculties of Medicine, Technology, Science and the Humanities, with the long term goal to develop neural interfaces (NI) for groundbreaking neurophysiological research on memory and learning in vivo and clinical applications that will improve quality of life for individuals with neurodegenerative diseases. We have therefore focused on NI constructs that have the potential of being implantable in humans and animals for long periods of time. Safety aspects and ethical issues are key aspects of the research. This includes safe and precise implantation techniques that cause minimal acute tissue damage, NI constructions that elicit minimal chronic tissue responses, NI with long life time, NI with a large number of electrodes that can be made to spread out in a controlled way inside deeply located targets to enable specific stimulation and NI that can be anchored so as to minimize micro-motions between NI and tissue. To this end, various types of ultra-thin, highly flexible anchor-equipped multichannel electrodes have been developed. From biocompatibility studies we have obtained evidence that such electrodes cause much less tissue destruction and less chronic tissue responses than other electrodes, key factors to obtain a normal neural milieu. Importantly, we can tailor these NI to the target tissue. These electrode constructions are embedded in a hard dissolvable support matrix. Special emphasis has been given to biocompatible matrix materials such as gelatin and hyaluronic acid. This way we have solved the problem of inserting ultrathin electrodes with preserved electrode architecture into soft tissue and accomplished a reduced tissue response as compared to e.g. stab wounds. By including matrix compartments with different dissolution times and different swelling factors the individual electrodes can be made to fan out inside the tissue, thereby targeting a highly specified region in the tissue. A short overview of these new NI will be given.

Useful Signals from Motor Cortex

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We are interested in the brain processes that subserve volitional movement. Our research program is divided into two areas; basic cortical mechanisms subserving arm movement and applied bioengineering of cortical output. The results of this basic research show that a large population of cells in frontal cortex, active during every arm movement, codes for details of the arm's trajectory (path of the hand through space and time). The prediction is accurate enough to recover the shape of drawn objects as well as many of the psychophysical characteristics of drawing. By extracting accurate trajectories from areas of the frontal cortex, we can probe perceptual processes, motor learning and latent input.

These brain-derived trajectory signals have also allowed us to develop a practical prosthetic application. Presently, monkeys are using these recorded signals to operate a robot arm to reach out and retrieve food for self-feeding without moving their own limbs. Results from this work show that subjects rapidly change their brain activity as they learn to control these devices. This work demonstrates human feasibility and we are pursuing further development of these techniques as we start trials in the coming year. We will begin with spinal cord injured subjects using advanced prosthetic arms and hands capable of performing everyday tasks that are dependent on dexterity with the hope that this technology will lead to a significant increase in quality of life for these individuals.

Cochlear and retinal prostheses: an overview of safety and efficacy, neural rescue and brain plasticity studies

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For more than 25 years research at the Bionic Ear Institute has focused on the ongoing development of cochlear prostheses for the severe-profoundly deaf. These devices have been implanted in more than 150,000 patient's world-wide and have regulatory approval for use in children as young as 6 months of age. More recently we have embarked - with colleagues from Bionic Vision Australia - on a program to develop a retinal prosthesis. I will provide an overview of the safety and efficacy studies required prior to clinical trials using examples from both projects. Specific objectives include the demonstration of: materials biocompatibility; safe surgical insertion (and reinsertion) of electrode arrays; acute electrophysiological studies to demonstrate spatially selective stimulation using safe stimulus intensities; chronic animal studies to evaluate safe electrical stimulation; long-term mechanical durability of the electrode/leadwire assembly; evaluating package hermeticity; and evaluating safety issues specific to the paediatric population.

In many applications neural prostheses electrically stimulate a gradually degenerating neural population. There is considerable interest in combining prosthetic devices with delivery of theraputic drugs designed to rescue target neurons. I will summarise our experimental studies delivering exogenous neurotrophins in combination with cochlear prostheses using a number of technologies including pumps, cell based therapies, viral vectors and nanoparticles.

In the final section of my talk I will provide a brief overview of our studies examining the use of cochlear prostheses to drive sensory plasticity. Using neonatally deafened animals – i.e. animals without prior auditory experience – we have demonstrated that long-term auditory input via a cochlear implant results in an auditory cortex that is functionally organised similar to that observed in normal hearing animals[1]. In contrast, the auditory cortex of neonatally deaf controls shows no evidence of that organisation.

[1] Fallon, Irvine & Shepherd. J Comp Neurol 512, 101-114 (2009).

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Development of neuromodulation treatments in a large animal model - Do neurosurgeons dream of electric pigs?

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The aim of our translational research is to examine mechanisms of action, and develop new treatment paradigms, of neuromodulation, in a large animal model.
Over the last 14 years the CENSE group has worked to established the Göttingen minipig as a research animal for neurological and neurosurgical disorders. The advantage of this animal is that it has a large gyrencephalic brain that can be examined at sufficient resolution using conventional clinical scanning modalities. The large brain, furthermore, enables the use of deep brain stimulation (DBS) electrodes and other neuromodulatory devices for human use, making the animal ideal for preclinical tests of new neuromodulation technology. The use of the Götingen minipig is economical and not associated with the ethical concerns associated with the experimental use of primates, cats and dogs.

In a minipig model of DBS towards Parkinsons disease we have examined mechanisms of action of this treatment with PET imaging. The model has been further developed with quantitative behavioral data and neurostereology. Minipig models of stem cell transplantation to the CNS has been established, to serve as a test platform for the in vivo characterization of stem cell lines developed towards neurodegenerative diseases and CNS cancer. The model also serves as a test system for new delivery systems for stem cell transferal to the CNS. The minipig model is being used to test encapsulated cell technology (ECT) for neurotrophic factor delivery in vivo. The studies have shown that the NGF or GDNF producing encapsulated cells survive implantation and explanation in their ECT device and that the neurotrophic factors diffuse out into the brain parenchyma from the ECT device in therapeutic amounts.

Studies concerning the possible role of Broadman 25 DBS for depression, hypothalamic DBS in the treatment of adiposity and pontine DBS toward central bladder regulation dysfunction are ongoing.

In conclusion the minipig provides a cost effective research model that allows validation of rodent data before clinical patient trials are initiated. The model also allows use and safety testing of neuromodulation equipment for human use. Finally it provides a platform for the examination of mechanisms of action of neuromodulatory treatments.

Nanochannels for cell biology and DNA analysis

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Nanotechnology is interesting because it enables the creation of tools on a size scale that is compatible with the basic components of life. We will discuss two examples to this end. Hollow nanowires can be made with diameters of 100nm and lengths on the scale of several micrometers. The small diameter ensures minimum perturbation when these nanosyringes are used to inject molecules into single cells. Basic fabrication schemes will be demonstrated along with preliminary results on transport of dye molecules into selected cells.

Nanofluidic channels with diameters on the scale of the persistence length of DNA can be used to stretch DNA. Once the DNA is introduced into the nanochannel it spontaneously stretches due to the excluded volume effect and due to the mechanical stiffness of the molecule. We will discuss recent developments in labeling of the DNA so that genomic information can be revealed by direct visualization of single DNA molecules.

A Biologically-based Strategy for Reducing the Foreign Body Response to Chronically Implanted Neural Interfaces

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As a starting point for a more principled approach to the design of penetrating microelectrode arrays intended for long-term use in brain tissue, we developed a computational model to explain the results of histological studies of the chronic brain tissue reaction to penetrating neural implants. The model assumes that the persistence of macrophages at the device brain tissue device interface creates a source of bioactive agents whose local concentration depends on device constitutive properties and the clearance characteristics of the adjacent tissue compartment. These agents which remodel local brain tissue include such factors as MCP-1, TNF-alpha, IL-1 beta, ROI's, and proteases; all known to be secreted by immune cells localized at the abiotic-biotic interface. Using published values of diffusivity, a finite difference model was used to simulate the distribution of such molecules around the surfaces of currently employed array technologies. Histopathological observations of implanted devices were used to refine and validate the model. Together they show that device geometry and permeability of the microelectrode array strongly influence the foreign body response. A similar analysis performed using virtually designed devices will properties more like brain tissue should improve the biocompatibility of penetrating microelectrode arrays.

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Cochlear implants: Matching the prosthesis to the brain and facilitating desired plastic changes in brain function

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A new approach to the design of cochlear implants and other sensory prostheses is described, in which the brain is regarded as a key (and variable) part of the overall system. In particular, the approach asks what the usually-compromised brain needs as an input in order to perform optimally, as opposed to the traditional approach of replicating insofar as possible the normal patterns of neural activity at the periphery. The traditional approach probably is perfectly appropriate for patients with a fully-intact brain, i.e., an ever-closer approximation to the normal patterns at the periphery is likely to provide the inputs the brain "expects" and is configured to receive and process. For patients with a brain compromised by years of auditory deprivation or a myriad of other causes, however, such inputs may not be optimal and indeed the compromised brain may not be able to "handle" or keep up with the complexity and rates of the inputs. Fundamentally different patterns of stimulation and responses at the periphery, e.g., far slower or far sparser or both, may be better. Patterns tailored to each brain's capabilities may allow the brain to gain a "foothold" in processing the (appropriately modified) inputs, which in turn may engage mechanisms of brain plasticity and thereby allow a growth in capabilities toward normal capabilities. If so, the patient might attain progressively higher levels of performance over time and might require periodic adjustments in the patterns of stimulation and responses at the periphery to provide optimal matches between the patterns and brain capabilities at all times, as the brain "reconfigures itself" through plastic changes. Ultimately, the patterns and the performance of the device may approach those for patients with fully intact brains from the outset, especially if the desired plastic changes in brain function and organization can be facilitated through well-timed adjustments in the patterns of stimulation and possibly through directed training to discriminate stimuli at the border of each patient's abilities at any given time. The previously mentioned foothold may be the essential first step toward high benefit from a sensory prosthesis for patients with initially compromised brains.

A polymer based multi electrode brain-machine interface

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Background The field of Brain Machine Interfaces offers new possibilities to treat a number of clinical conditions such as chronic pain, motor disorders such as Parkinsons disease and essential tremor as well as controlling prosthesises. So far, the field has been focused on wire arrays and more or less rigid silicon and/or polymer probes. Our group is involved in developing tailor-made neural interfaces to specific Brain centers. We have previously developed a highly flexible electrode array for cerebellar cortex based on SU-8 with gold leads. The aim of the present work is to further improve the properties of the interface by expanding the number of electrodes on each chip and modifying the surface of the recording sites to reduce their impedance.

Method and Results A novel 9-electrode probe designed for several different cell layers (molecular cell layer, purkinje cell layer and granular cell layer) of the cerebellum was devolved. SU-8 was chosen as the bulk material for the probe because it is photo structurable, relatively flexible compared to silicon and known from other biological applications. The electrode probes (8 µm thick) were fabricated as a sandwich structure with gold as conductor and electrode material and SU-8 as insulating bulk material. Furthermore, the probe was designed with anchor structures to enable fixation of the electrode position. Also, to increase electric performance Platinum black, a surface area increasing coating, were platinised onto the electrodes using an electrolyte containing 1 % chloroplatinic acid, 0.0025 % hydrochloric acid and 0.01 % lead acetate.

Conclusion A probe with 9 platinum black coated electrodes has been fabricated. The fabrication process allows easy change of the electrode design, such as number of electrodes, spatial resolution of electrodes, size and material of the electrodes. Coating the electrode sites with platinum black lowered the the impedance by up to a factor 100. This, in turn, will allow us to reduce the size of the electrodes further, thus opens up possibilities to record from very small neurons and dendrites.

UV-B irradiation affects nociceptive C fibre input to the primary somatosensory cortex

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Most animal studies of nociceptive transmission have assessed different types of behavioural and reflex responses. However, the validity of motor responses in predicting pain and analgesia is not always clear, as these might be channelled through pathways other than those signalling nociceptive information to the sensory cortex cerebri. The aim of the present study was to evaluate if UV-B induced hyperalgesia, known to produce hyperalgesia in behavioural tests, is reflected in corresponding changes in nociceptive transmission to primary somatosensory (SI) cortex.

Recordings of evoked potentials in forelimb and hind limb SI cortex from the irradiated, nearby and distant skin areas were commenced under anaesthesia 20–24 h after UV-B irradiation. The dose (1300 mJ/cm2) caused reddening of the skin and decreased nociceptive reflex threshold. Averaged (n = 16) recordings were used for analysis. The area under curve (AUC) was defined as the magnitude of the late evoked potentials. Tramadol hydrochloride (2 mg/kg, i.v.) was administered to determine whether the UV-B effect on laser evoked potentials (LEPs) could be reversed.

CO2 laser stimulation regularly evoked late surface positive potentials in SI cortex, previously shown to be due to input from C fibres (LCEP). A significant decrease in onset latency and increase in duration of the LCEP from the irradiated skin areas was observed after UV-B irradiation, whereas no significant increase in magnitude was found. In contrast, the onset latency and duration of LCEPs elicited from nearby non-irradiated (secondary hyperalgesic) skin areas were unaltered, while the AUC of the LCEPs was potentiated strongly. Furthermore, distant skin regions (forepaw) elicited LCEPs that were significantly delayed and tended to be reduced in magnitude. Tactile evoked potentials were not affected after UV-B irradiation. Tramadol reduced the UV-B-induced changes related to secondary hyperalgesia, but had little effect on primary hyperalgesia or on LCEPs elicited from distant skin.

The UV-B-induced hyperalgesia is reflected in the nociceptive transmission to SI cortex and is a promising model of hyperalgesia.

Ethics, Deep Brain Stimulation and Major Depressive Disorder

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Within bioethics there has in recent years been an increasing interest in the ethical implications of deep brain stimulation (DBS), and lately the first articles on DBS and psychiatric disorders such as depression have appeared. DBS, commonly referred to as a brain pacemaker or a neurostimulator, is a surgical treatment where chronic invasive electrodes stimulate brain structures deep within the brain. Initially DBS was used as a last resort treatment for movement disorders such as Parkinson's disease and essential tremor as well as relieving chronic pain. Today its use is extended. Beside attempts to treat migraine, epilepsy and balance disorders, studies have been conducted to evaluate DBS as a treatment of for instance Tourette's syndrome, obsessive compulsive disorder and major depressive disorder. Further, the technique is considered as a possible treatment for anorexia, obesity, cocaine addiction, memory disorders and aggression, which is likely to spur the ethical discussion even further.

Intervening in the brain raises both hopes and worries, especially when the treatment targets moods, emotions and behaviour, all which are closely connected to a person's personality. While the hopes lay in finding a remedy for the millions of people worldwide who suffer from treatment-refractory depression, among whom roughly 15% will commit suicide, it is essential to make sure that the therapy lives up to face value before it is used on a larger scale. At present there are still vast knowledge gaps calling for caution, both regarding the use of DBS in general, and particularly when the technique in employed on a psychiatric disorder. For instance, could the therapy result in unacceptable personality changes, as were the case with many of the patients who underwent lobotomies?

This poster gives an overview of some of the key ethical concerns regarding DBS as a therapy for treatment-refractory major depressive disorder, where a multidimensional approach is employed to capture the wide range of ethical facets raised by this novel intervention. Not only must the medical concerns be acknowledged, intervening in the brain – especially if the brain is depicted as "the organ of the mind" - can raise social, political and religious concerns of ethical importance as well. In addition, both possible gains and risks of harm are identified.

Polystyrene casts of neuron basal lamina for guidance of axons

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Various scaffolds have been used for neural repair and axon guidance. Basal lamina of the Schwann cell constitutes the outer boarder surrounding each nerve fiber within a nerve. It is built up mainly of laminin heterotrimers, collagens, entactin and proteoglycans. Basal lamina scaffold obtained through extraction of nerves or extracted nerve segments can be used substrates for regenerating axons. Here we tested if casts of such preparations could be used to guide axonal outgrowth. To this end, longitudinal um-thick sections of rat sciatic nerve were extracted for myelin resulting in acellular basal lamina master copy with lined up grooves. From the basal lamina master a reversed Polydimethylsiloxane (PDMS) copy was made. Then a correctly mirrored polystyrene copy was made from the PDMS copy. The polystyrene copy showed high similarity (to the master copy) within an nm frame using scanning electron microscope. Mouse dorsal root ganglions were then grown on top of copy and compared to growth on the extracted nerve segment (master copy). The orientation of the regenerating axons was evaluated mathematically 4-5 days later using the Fourier transformation on B-III-tubulin stained preparations. An orientation was found. The axons followed the direction of basal lamina, both the original and polystyrene copy. Thus with fairly simple methods we can make functional copies of basal lamina.

A laser milled gelatine matrix for implanting a polymer-based microelectrode array

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Background
The field of Brain Machine Interfaces (BMI:s) has been centred on wire arrays and more or less rigid silicon and/or polymer probes. We have previously shown a novel electrode array for chronic neural interfaces based on SU-8 with gold leads yielding acute recordings of very high quality in the cerebellum of cat. Moving on to chronic recordings and introducing a sheddable gelatin matrix for improved insertion, this study aims to show the feasibility of the array as a platform for chronically interfacing the brain.

Methods
Our current focus has been on implanting SU-8 arrays with multiple gold leads in the cerebellar cortex of Sprague-Dawley rats for chronic recordings of neuronal activity. To facilitate the insertion of the extremely thin and flexible arrays, they were imbedded in a 100 µm thick gelatine film matrix that was cut into the shape of a needle using a high-precision UV laser milling tool. This process increased stiffness and ability to penetrate the pia mater of the CNS. Multielectrode arrays were implanted during fentanyl anaesthesia and fastened to the skull with dental cement. The wound was closed around the dental cement, leaving a transcutaneous connector for the recording sessions. Recordings were obtained from post implantation day 1 and onwards under ketamine/xylazine anaesthesia. Using this setup, both spike and field potential activity of the cerebellum was collected without electrical filtering or mechanical stabilization.

Conclusion
The implantation was substantially improved using the gelatin embedding technique described. The recordings obtained were of high to acceptable quality even lacking the electrical filtering commonly used in chronic electrophysiological recordings. Field potentials recorded after electrical stimulation of the appropriate receptive field of the rat skin showed well defined mossy fiber axon volleys, synaptic activation of granule cells by mossy fibers and climbing fiber activation of Purkinje cells. In addition, we obtained recordings from unitary fast spikes. This shows the array design performs as expected in vivo.

Gelatine-embedded electrodes – A novel biocompatible vehicle allowing implantation of highly flexible microelectrodes

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Chronic neural interfaces that are both structurally and functionally stable inside the brain over years or decades hold great promise to become an invaluable clinical tool in the near future. A key flaw in the current electrode interfaces is that their recording capabilities deteriorate over time, possibly due to the lack of flexibility, which causes movements in relation to the neural tissue that result in small inflammations and loss of electrode function. We have developed a new neural probe using the stabilizing property of gelatine that allows the implantation of ultra-thin and flexible electrodes into the central nervous system. The microglial and astrocytic reactions evoked by implanted gelatine needles, as well as the wire bundles in combination with gelatine, were investigated using immunohistochemistry and fluorescence microscopy up to 12 weeks after implantation. The results indicate that pure gelatine needles were stiff enough to penetrate the brain tissue on their own, and evoked a significantly smaller chronic scar than stab wounds. Moreover, gelatine embedding appeared to reduce the acute reactions caused by the implants and we found no adverse effects of gelatine or gelatine-embedded electrodes. Successful electrophysiological recordings were made from 7.5 µm thick electrodes implanted in this fashion.

Using Non-Invasive BMI for Cognitive Enhancement Via Emotion Feedback

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Low cost, consumer-grade EEG technologies are becoming available in the form of portable wireless systems that may integrate additional psychophysiological measurements (e.g. GSR and EMG). Unlike heavier and more expensive brain imaging technologies, these EEG systems have the potential for being used in the creation of enhanced or augmented cognition systems in a broad range of application environments.

Our current work has a particular interest in the use of BMI data as a foundation for learning emotion regulation to improve performance in what may be intense decision situations. Hemispherical asymmetry is associated with emotional valence; higher right hemisphere activation correlates with withdraw behaviours associated with negative emotions, while higher left hemisphere activation correlates with approach behaviours associated with positive emotions. Additional psychophysiological data (GSR and EMG) can be used to provide greater discrimination within these broad emotional categories. Also, the classic EEG wave categories Alpha (relaxed, reflective, inhibited) and Beta (alert, anxious, concentrating) may provide a foundation for learning mindfulness.

We are exploring the use of these measures to provide real time inputs to technological systems supporting emotion regulation and mindfulness within the application domain of stock trading. This work is based upon empirical data providing evidence that better trader performance is associated with the ability to be less influenced by emotions during decision processes. EEG may provide a foundation for minimising emotions as revealed by hemispherical asymmetries, raising Alpha wave levels, and reducing Beta wave levels. These measures may be used to produce digital perceptual feedback to provide input to cognitive emotion regulation training on the part of human decision makers. Alternatively, it may be possible to automatically adapt task support systems to favour target emotional states, creating enhanced cognitive performance by externally controlled emotional regulation, shifting learning to the machine. More invasive technologies could greatly improve such a system.

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Conducting Polymer 3D Microelectrodes for neurobiological studies

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Utilising non-organic microelectrodes for neurobiological studies can pose some issues such a poor biocompatibility and biofouling. In this work we will present the use of conducting polymer 3D microelectrodes have been fabricated especially for use in neurological applications. A combination of micro-fabrication techniques and chemical polymerization methods has been used to create pillar electrodes in polyaniline and polypyrrole. The thin polymer films obtained showed good uniformity and adhesion to both horizontal and vertical surfaces. The electrodes with the combination of metal/conducting polymer materials have been characterized by electrochemically and has shown evidence of enhanced electrochemical activity by over a factor of 10 when compared with electrodes coated with only metal. An electrochemical characterization of gold/polypyrrole electrodes showed exceptional electrochemical behaviour and activity, making the structures suitable for future in-vitro neurological measurements.

Organic electronics toward artificial neurons

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Breakthroughs in the understanding of brain function, both in terms of healthy activity and neurological disorders, have necessitated the development of new techniques to interface machines with the brain. Attempts to realize such an interface are commonly based on direct electrical stimulation and sensing or exogenous drug delivery. While these efforts have proven fruitful, they suffer from a variety of drawbacks, for example, electrical methods' inability to discriminate amongst cell types, or the difficulty in controlling the dynamics of localized drug delivery. Indeed, few techniques have attempted to mimic the neuron's own combination of electronic and chemical signaling. Here we demonstrate the organic electronic ion pump (OEIP), a technology which aims to accomplish just such neural biomimicry: electronically modulated delivery of ions, neurotransmitters and other bio-substances. Based on electrophoretic migration through an organic electronic polymer system, delivery is diffusive and non-convective, that is, without fluid flow. In a variety of geometries, OEIP technology can be used in vitro, for example, for neuronal cell-signaling studies by direct delivery into the cellular microenvironment. In an encapsulated form, the OEIP has been used in vivo to modulate sensory function in a living animal. In its present form, the OEIP has demonstrated its usefulness as a tool for neural system interfacing. As a first step towards an "artificial neuron", it has significant potential as both a research tool and a therapeutic platform for the treatment of various neurological disorders.

Nanowire based electrodes for neuronal signal recording

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Research on neural interfaces may open up new possibilities for basic research and clinical applications. Nanostructured interfaces for neuronal signal recording have been proven to give better spatial resolution and lower impedance. The goal of our study is to develop a model system for studying nanostructured neuronal interfaces for electrical signal recordings.

Periodic arrays of free standing vertical gallium phosphide nanowires epitaxially grown from (111)B gallium phosphide surface are used as a scaffold for neural electrodes. The nanowires can be synthesized with high aspect ratio and very little tapering. The nanowire arrays are defined using electron beam lithography and grown with metal organic vapor phase epitaxy with high degree of control over the nanowire array geometry. A thin layer of hafnium oxide is used to improve mechanical properties of nanowires. The nanowire based electrodes have a sandwich like structure with a gold conducting layer and a photosensitive polymer as the insulator.

We believe that the nanowire electrodes will provide a model system for probing different effects of nanostructures on neuronal signal recordings and will allow recordings from very small neuronal elements, such as synapses and dendrites.

Micro and nanoelectrodes for Neurological studies

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The fusion of cell biology with nanotechnology opens up new possibilities within the frontier of understanding complex biological processes. Here we present a combined effort between neuroscience and nanotechnology to investigate how to utilise micro and nanotechnology to within neuroscience. The overall idea of integrated micro and nanosystems for use in neuroscience will be presented, including on chip culturing of cells and brain slices, electronic interface systems utilising 2D and 3D electrode for probing neurological dynamics. Finally a conclusion of preliminary results will be presented, and a discussion of the vision for the future will also be given.

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Three dimensional electro and electrochemical systems for neurobiological studies

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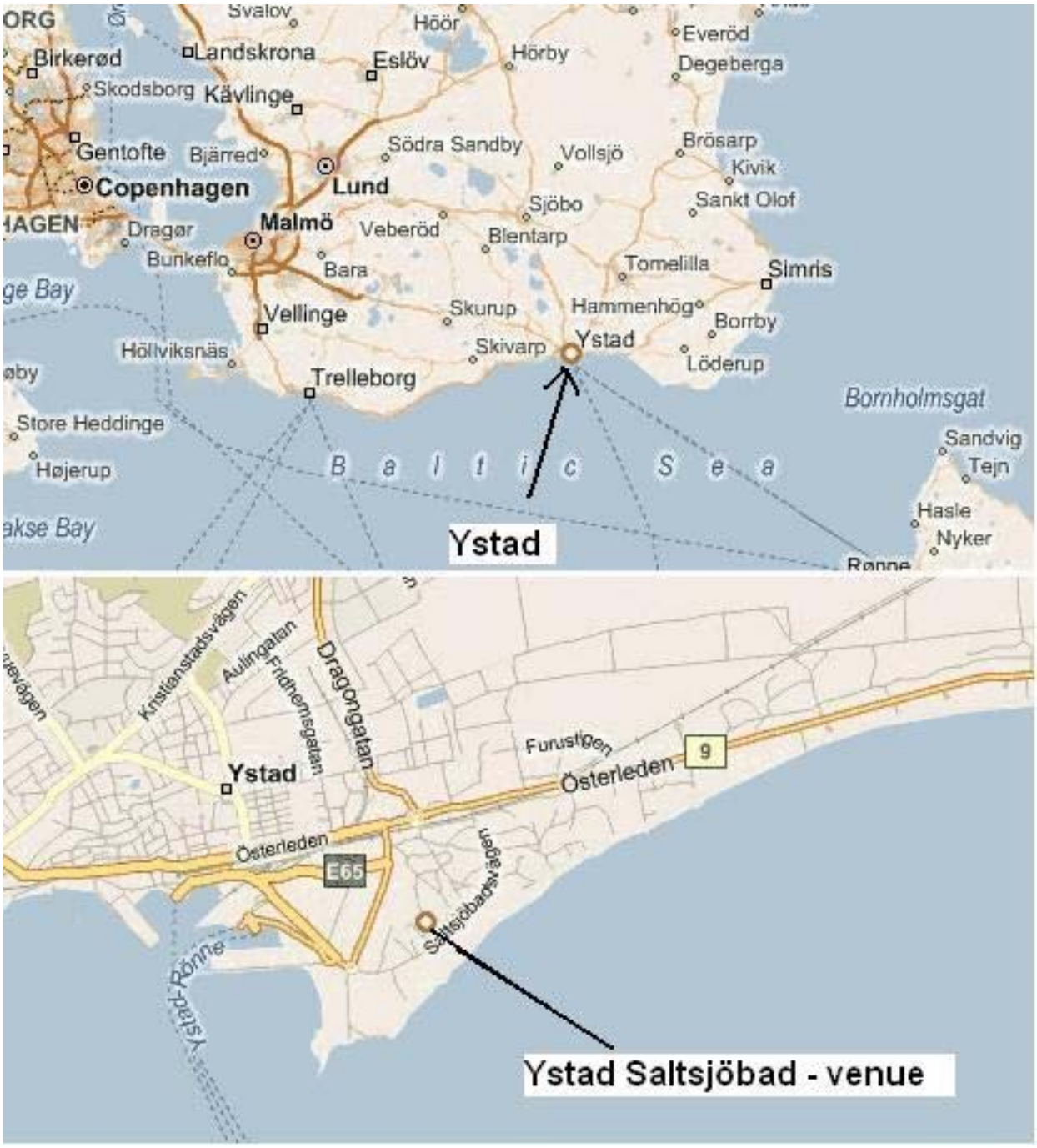
In this work we report a novel three dimensional electrode array for electrical measurements in neuronal studies. The main advantage of working with these out-of-plane structures is the enhanced sensitivity of the system in terms of measuring electrochemical changes in the environment of a cell culture in real time. In addition, the system is devised to offer a compact solution that helps to obtain a homogeneous distribution of current density among the active electrodes. The first result illustration the potential for these electrodes will be pretend and discussed.



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