NeuroIT.net/EC
Information Workshop

Bidirectional Neural Interfaces

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Bruxelles, January 16, 2007

Outline of the talk

- Definition of (invasive) bidirectional neural interfaces
- Motivations for the development of neural interfaces
- Neural interfaces with the central nervous system
- Neural interfaces with the peripheral nervous system
- Conclusions

Outline of the talk

☐ Definition of (invasive) bidirectional neural interfaces

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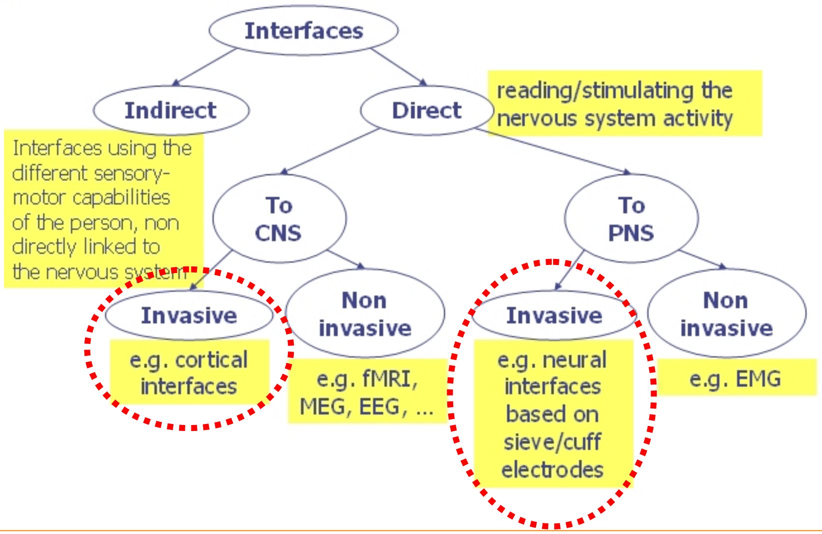
(Invasive) Neural Interfaces

(Bio)artificial devices able to (re)create a bidirectional natural link with the (central and peripheral) nervous system

Nerve fibres are not “wires'' or “cables'' in the engineering point of view, but long, sensitive structures consisting of biological membranes with multiple receptors and delicate interactive elements for on-line sensing the environment and transmitting information via molecules, potentials and changes in the chemo-electrical activity

(Heiduschka and Thanos, Progress in Neurobiology, 1998)

(Invasive) Neural Interfaces



Outline of the talk

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☐ Motivations for the development of neural interfaces

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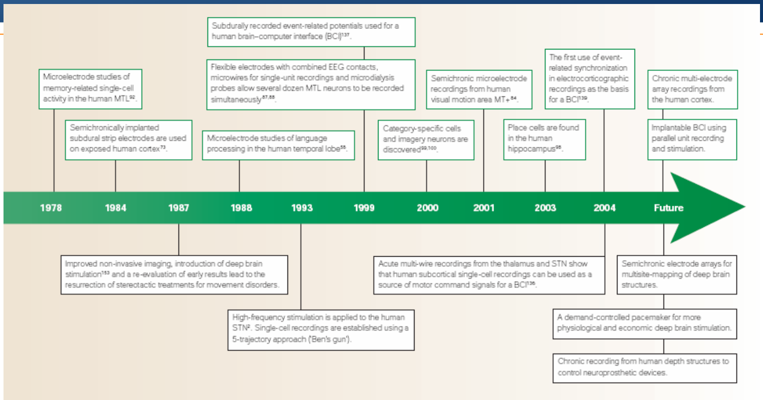
Neuroscientific motivations



1978: Microelectrode studies of memory-related single-cell activity in the human MTL[92].

1984: Semichronically implanted subdural strip electrodes are used on exposed human cortex[73].

1987: Improved non-invasive imaging, introduction of deep brain stimulation[153] and a re-evaluation of early results lead to the resurrection of stereotactic treatments for movement disorders.

1988: Microelectrode studies of language processing in the human temporal lobe[58].

1993: High-frequency stimulation is applied to the human STN[2]. Single-cell recordings are established using a 5-trajectory approach ('Ben's gun').

1999: Subdurally recorded event-related potentials used for a human brain–computer interface (BCI)[137].

1999: Flexible electrodes with combined EEG contacts, microwires for single-unit recordings and microdialysis probes allow several dozen MTL neurons to be recorded simultaneously[87,88].

2000: Category-specific cells and imagery neurons are discovered[99,100].

2001: Semichronic microelectrode recordings from human visual motion area MT+[84].

2003: Place cells are found in the human hippocampus[95].

2004: The first use of event-related synchronization in electrocorticographic recordings as the basis for a BCI[139].

2004: Acute multi-wire recordings from the thalamus and STN show that human subcortical single-cell recordings can be used as a source of motor command signals for a BCI[136].

Future: Chronic multi-electrode array recordings from the human cortex.

Future: Implantable BCI using parallel unit recording and stimulation.

Future: Semichronic electrode arrays for multisite-mapping of deep brain structures.

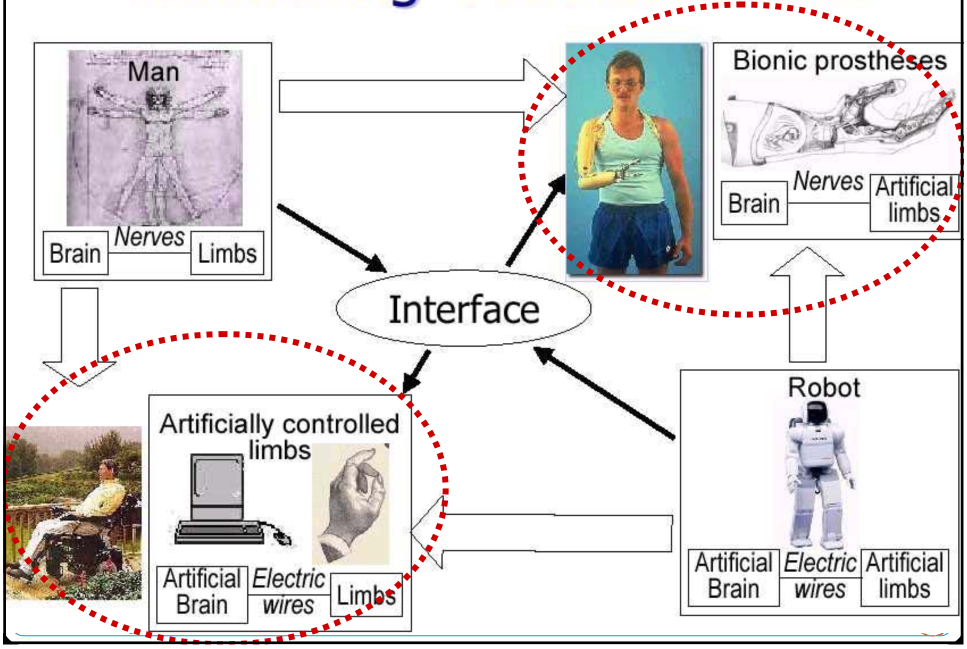
Future: A demand-controlled pacemaker for more physiological and economic deep brain stimulation.

Future: Chronic recording from human depth structures to control neuroprosthetic devices.

Although non-invasive methods such as functional magnetic resonance imaging, electroencephalograms and magnetoencephalograms provide most of the current data about the human brain, their resolution is insufficient to show physiological processes at the cellular level

Engel et al., Nature Rev Neurosc, 2005

"Connecting" Man and Robot



Man
Brain
Nerves
Limbs

Bionic prostheses
Brain
Nerves
Artificial limbs

Interface

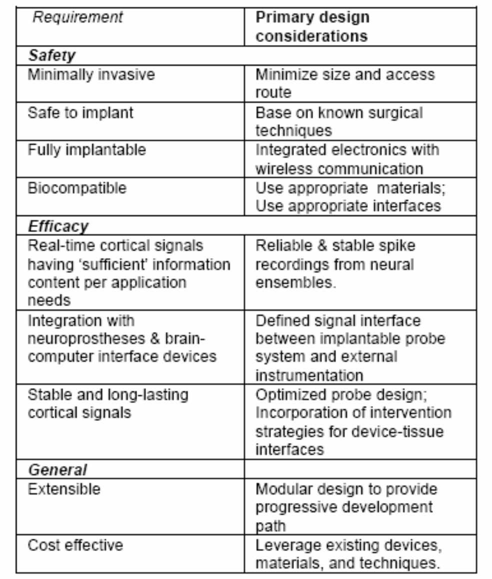
Artificially controlled limbs
Artificial Brain
Electric wires
Limbs

Robot
Artificial Brain
Electric wires
Artificial limbs

Outline of the talk

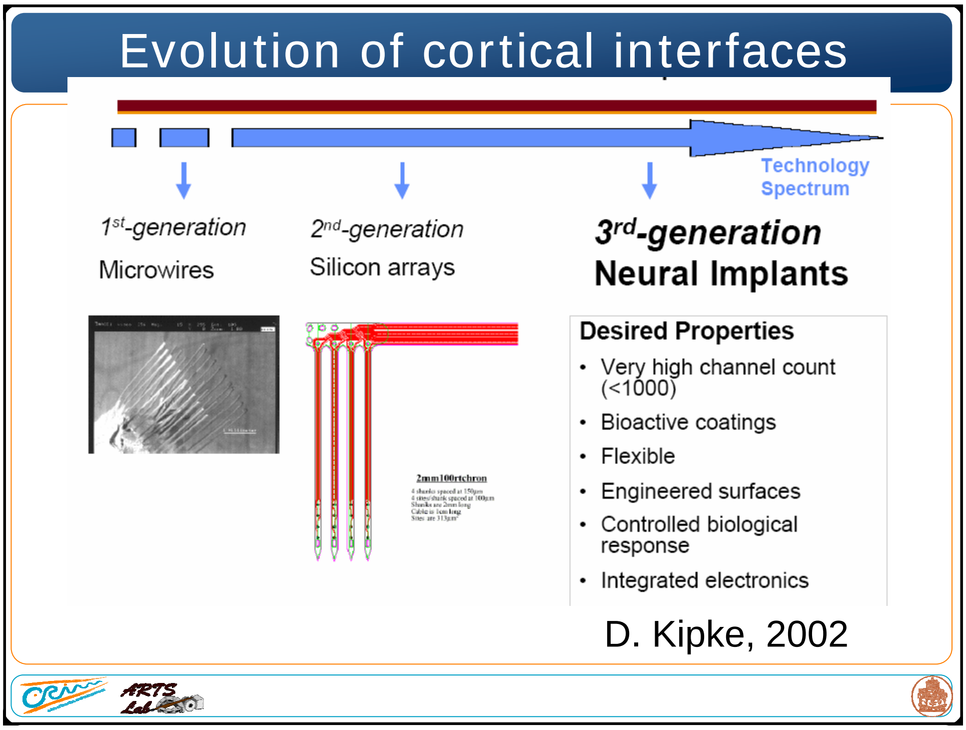
- Neural interfaces with the central nervous system

Requirements for (cortical) neural interfaces



Requirement	**Primary design considerations**
Safety	
Minimally invasive	Minimize size and access route
Safe to implant	Base on known surgical techniques
Fully implantable	Integrated electronics with wireless communication
Biocompatible	Use appropriate materials; Use appropriate interfaces
Efficacy	
Real-time cortical signals having 'sufficient' information content per application needs	Reliable & stable spike recordings from neural ensembles.
Integration with neuroprostheses & brain-computer interface devices	Defined signal interface between implantable probe system and external instrumentation
Stable and long-lasting cortical signals	Optimized probe design; Incorporation of intervention strategies for device-tissue interfaces
General	
Extensible	Modular design to provide progressive development path
Cost effective	Leverage existing devices, materials, and techniques.

Kipke, IEEE EMBS, 2004



Evolution of cortical interfaces

1st-generation
Microwires

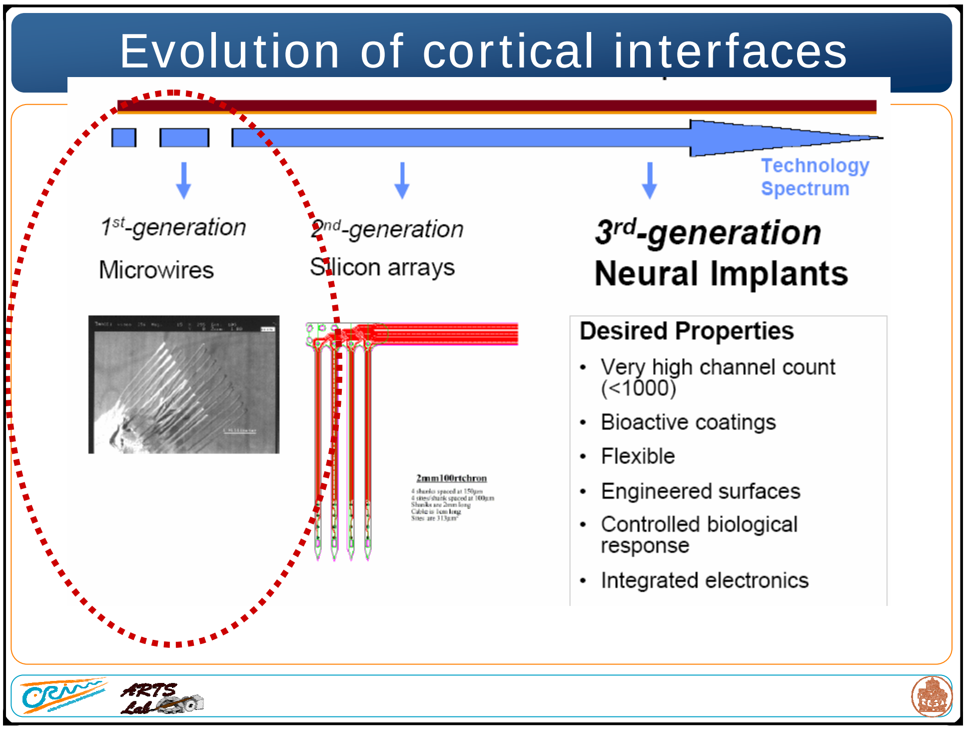
2nd-generation
Silicon arrays

3rd-generation
Neural Implants

Desired Properties

- Very high channel count (<1000)
- Bioactive coatings
- Flexible
- Engineered surfaces
- Controlled biological response
- Integrated electronics

D. Kipke, 2002



Evolution of cortical interfaces

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Cortical interfaces – 1st generation

Wise et al.,
Proc IEEE, 2004

- Traditional metal microelectrodes are electrolytically sharpened wires (pins), 25 to 50 µm in diameter and insulated to define an exposed recording area at the tip of perhaps 100 μm^2
- Such electrodes record the local voltage associated with ionic current flow around a neuron when it fires in response to inputs received from other cells
- The electrode sites are capacitive with an impedance of a few megohms at 1 kHz
- Recorded signals range from the noise level (20 µV or so) to about 1 mV, with an extracellular signal bandwidth of perhaps 10 kHz

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Cortical interfaces – 1st generation

Limits of the first generation of cortical interfaces:

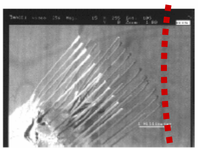
- Reduced reproducibility of the shape of the interfaces
- Damages provoked while implanting the electrodes
- Problems in the localization of the recording sites because of the tendency of the interfaces to change their relative position after the implant

Evolution of cortical interfaces

Technology Spectrum

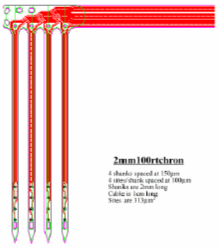
1st-generation

Microwires



2nd-generation

Silicon arrays



3rd-generation

Neural Implants

Desired Properties

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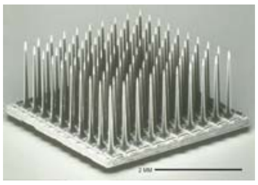
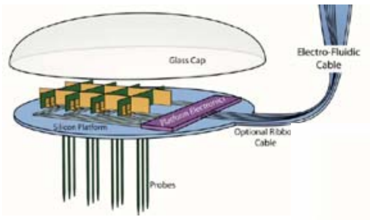
Cortical neural interfaces – 2nd generation

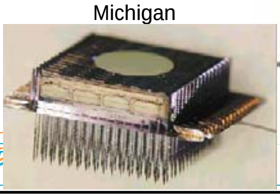
They exploit the potentials of microfabrication techniques

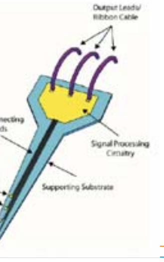


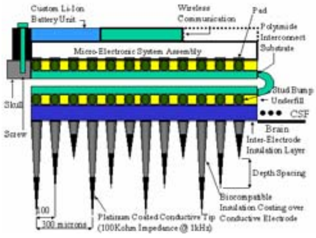
Utah Array, Bionic Technologies



University of Michigan

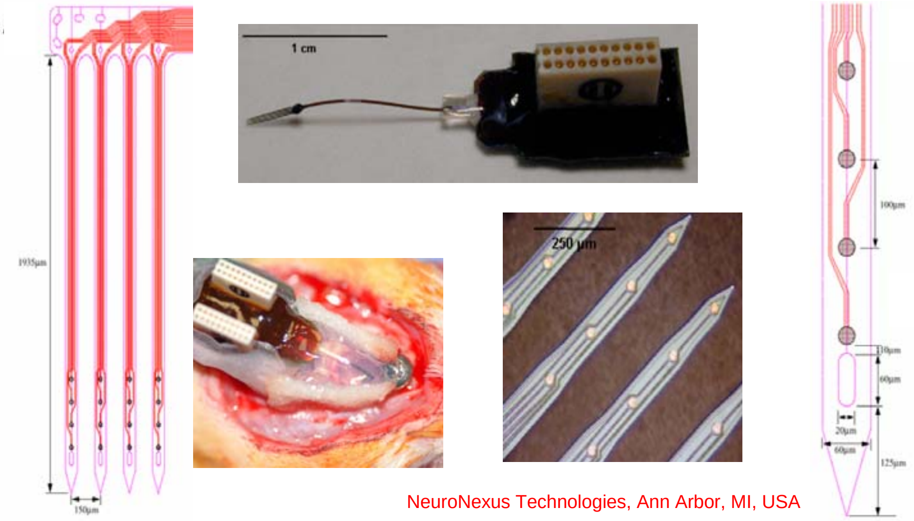






MIT Bioinstrum Lab

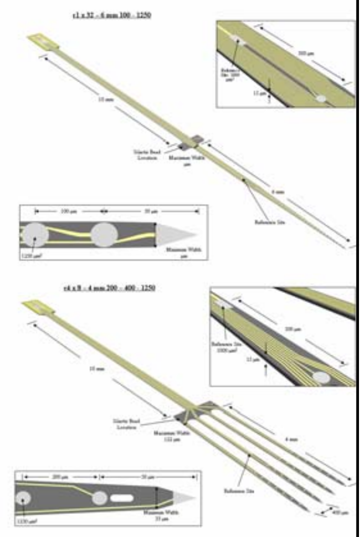
Michigan silicon probe (MSP)

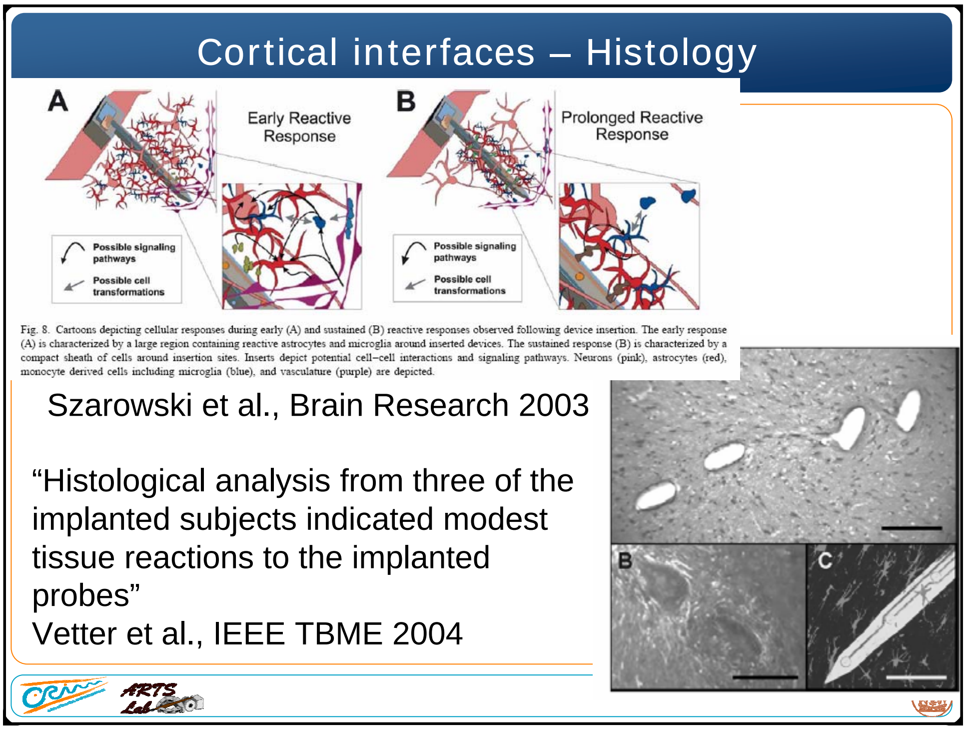


NeuroNexus Technologies, Ann Arbor, MI, USA

Characteristics

- One shank, with multiple sites, that is about the size of a conventional wire electrode
- Batch fabricated
- High reproducibility of geometrical shape, electrical properties, and mechanical properties
- Easy customization of site placement and substrate shape
- Small size, resulting in minimal displacement of the neural tissue
- High spatial resolution at various depths up to 1cm
- Multiple parallel shanks, providing horizontal spatial sampling
- Independent recording/stimulation among sites
- Higher data output with fewer animals



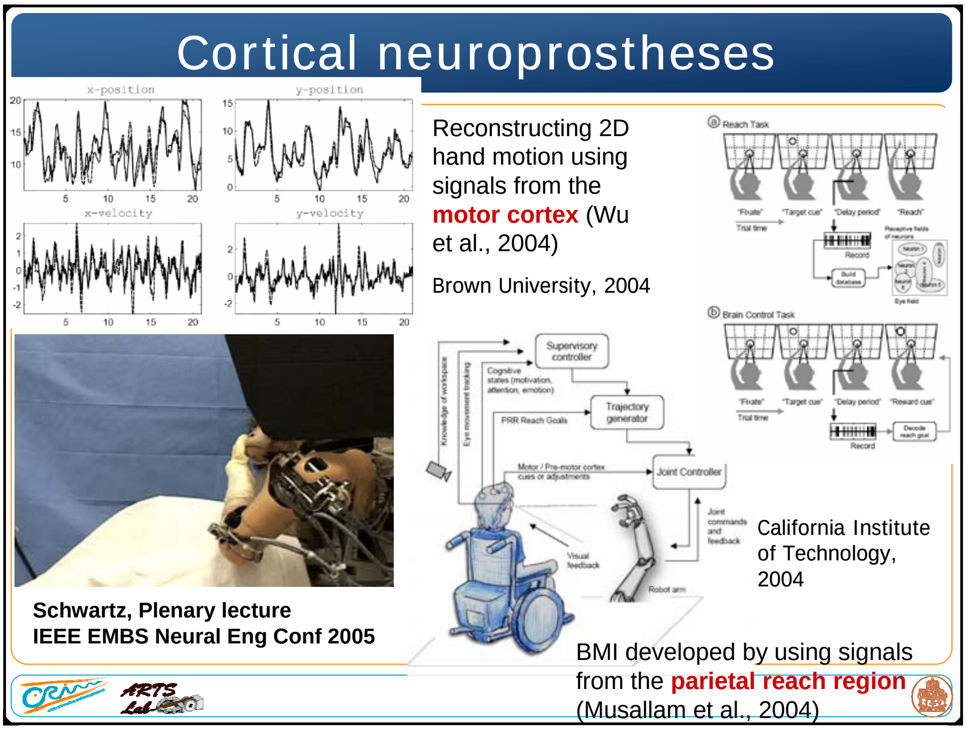


Cortical interfaces – Histology

Fig. 8. Cartoons depicting cellular responses during early (A) and sustained (B) reactive responses observed following device insertion. The early response (A) is characterized by a large region containing reactive astrocytes and microglia around inserted devices. The sustained response (B) is characterized by a compact sheath of cells around insertion sites. Inserts depict potential cell–cell interactions and signaling pathways. Neurons (pink), astrocytes (red), monocyte derived cells including microglia (blue), and vasculature (purple) are depicted.

Szarowski et al., Brain Research 2003

“Histological analysis from three of the implanted subjects indicated modest tissue reactions to the implanted probes”
Vetter et al., IEEE TBME 2004



Cortical neuroprostheses

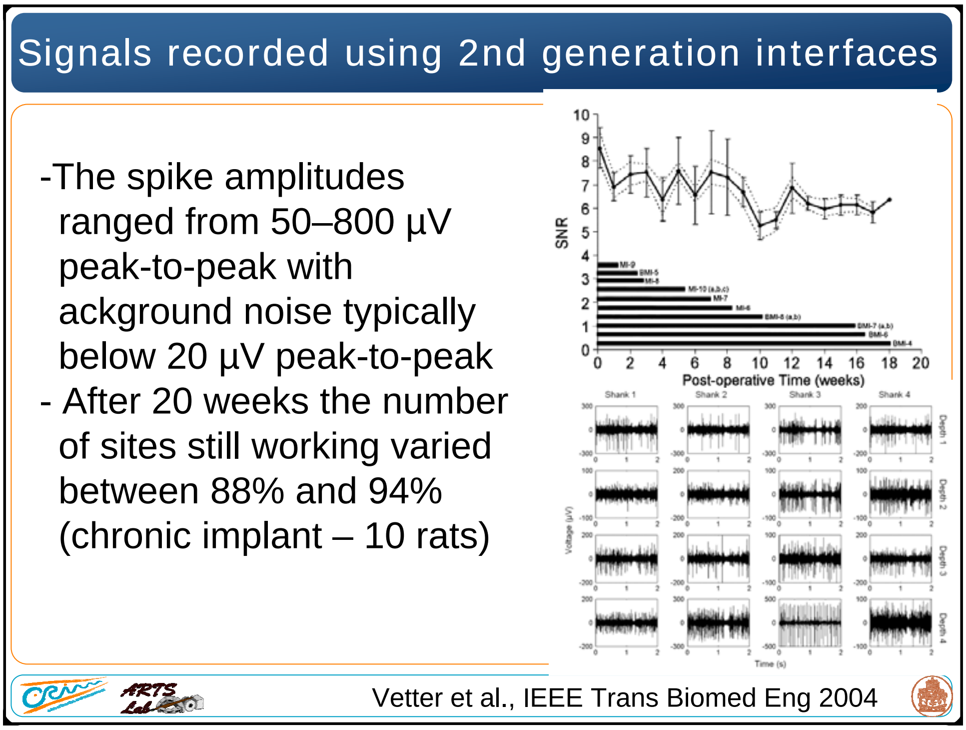
Reconstructing 2D hand motion using signals from the **motor cortex** (Wu et al., 2004)

Brown University, 2004

California Institute of Technology, 2004

BMI developed by using signals from the **parietal reach region** (Musallam et al., 2004)

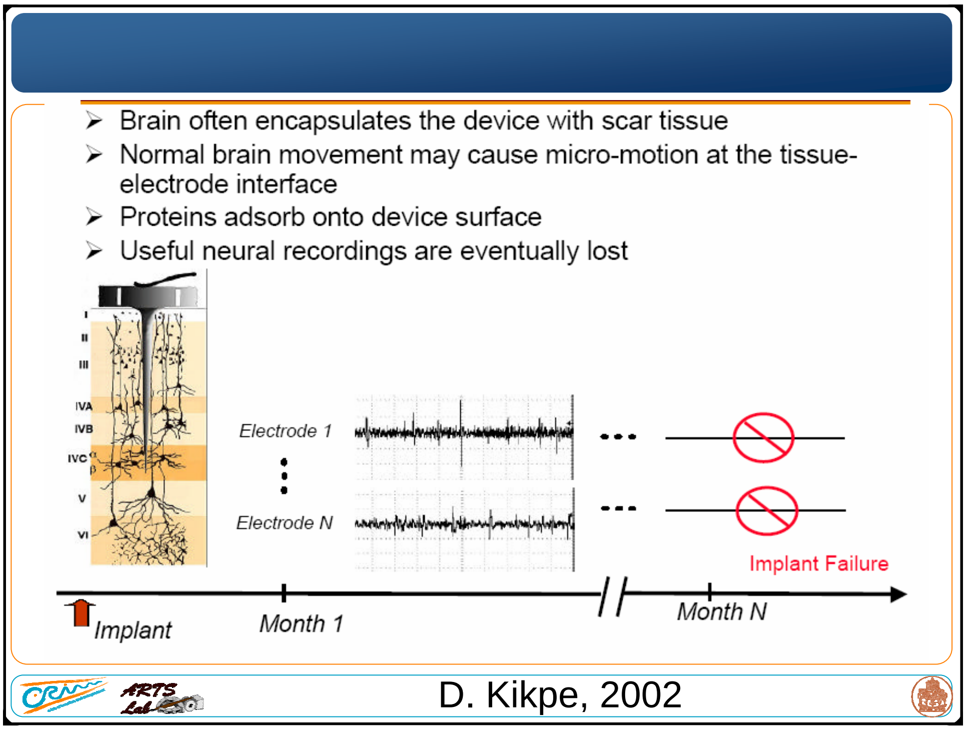
Schwartz, Plenary lecture
IEEE EMBS Neural Eng Conf 2005



Signals recorded using 2nd generation interfaces

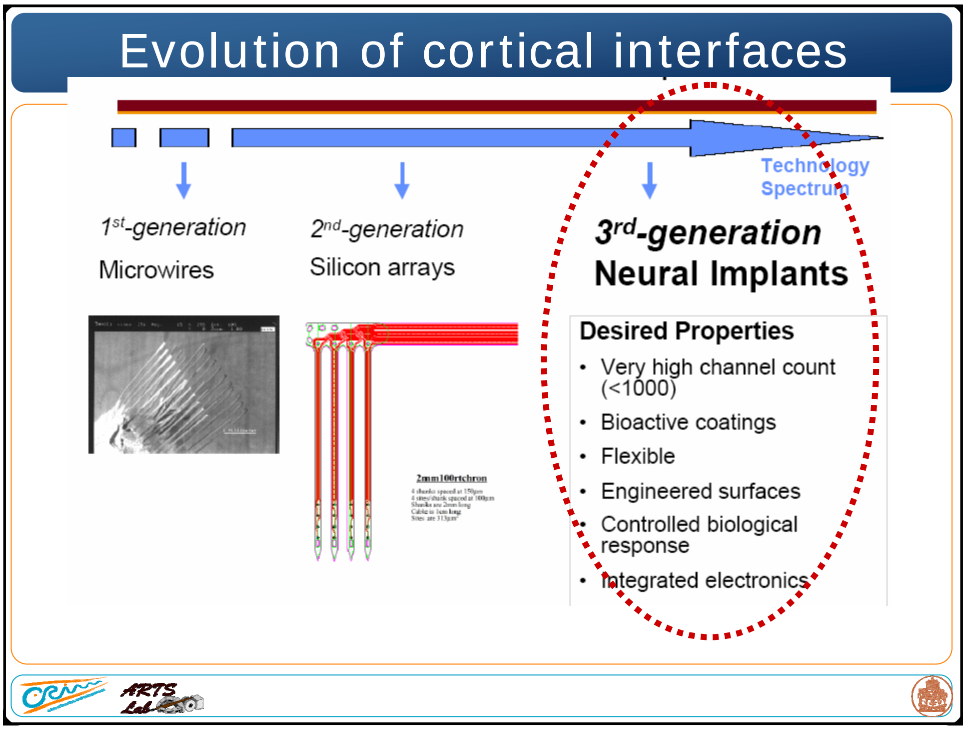
-The spike amplitudes ranged from 50–800 µV peak-to-peak with ackground noise typically below 20 µV peak-to-peak
- After 20 weeks the number of sites still working varied between 88% and 94% (chronic implant – 10 rats)

Vetter et al., IEEE Trans Biomed Eng 2004



- Brain often encapsulates the device with scar tissue
- Normal brain movement may cause micro-motion at the tissue-electrode interface
- Proteins adsorb onto device surface
- Useful neural recordings are eventually lost

D. Kikpe, 2002



Evolution of cortical interfaces

Technology Spectrum

1st-generation

Microwires

2nd-generation

Silicon arrays

3rd-generation

Neural Implants

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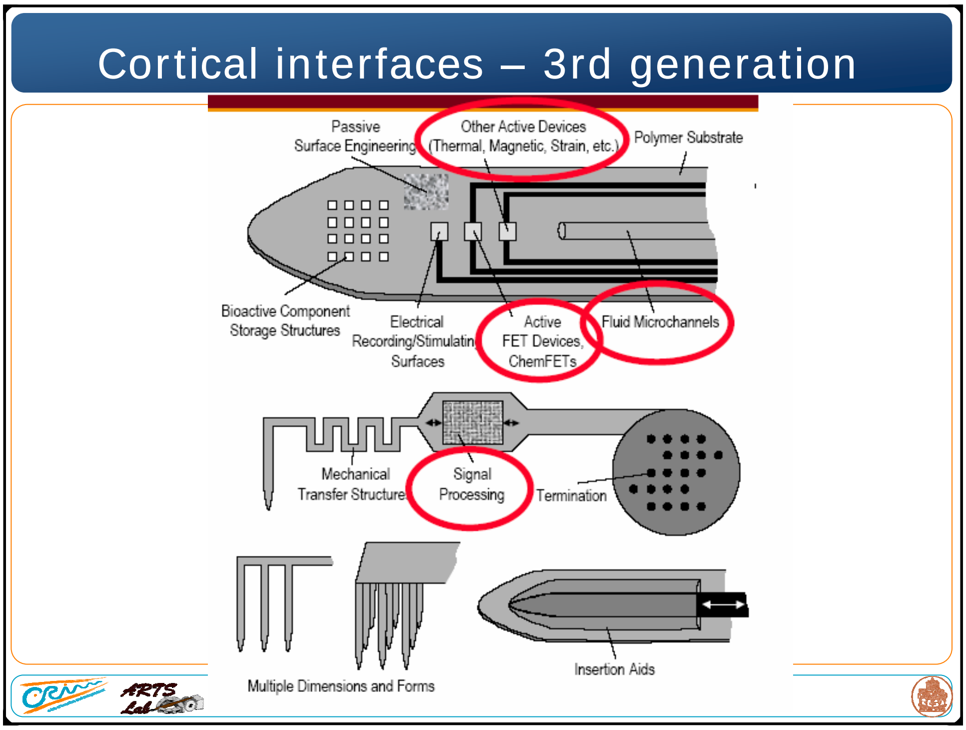
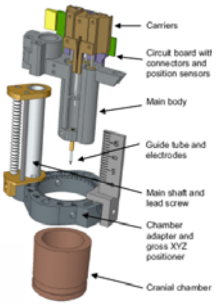
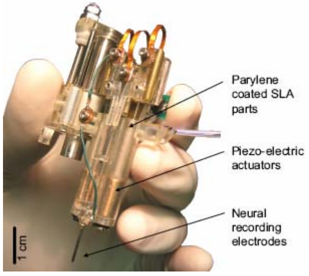


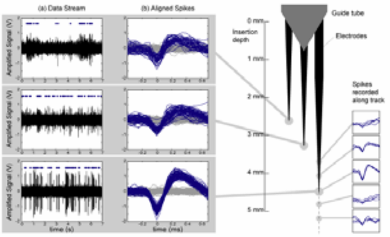
Cortical interfaces – 3rd generation

Actuated cortical interfaces

- A prototype neural interface “microdrive” capable of positioning electrodes with micron precision to record signals from active neurons
- The prototype is constructed using a layered manufacturing (rapid prototyping) method and made bio-compatible through coating of Parylene



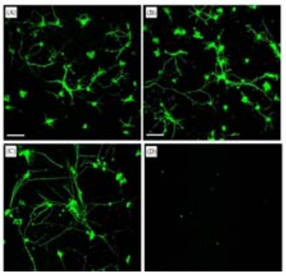


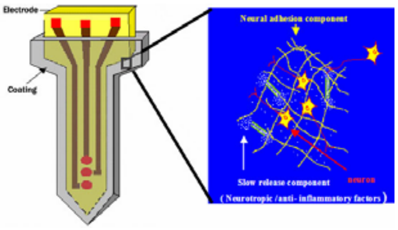


Cham, Burdick, Andersen et al., Proc. BIOROB 2006

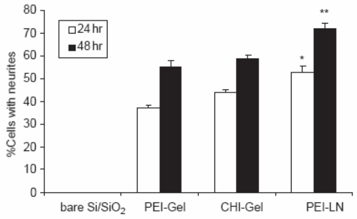
Coating of neural interfaces

- Biocompatible coatings are used to improve the integration/adhesion between the nervous system and the electrodes
- This approach should increase the lifetime of the neurons reducing local inflammations



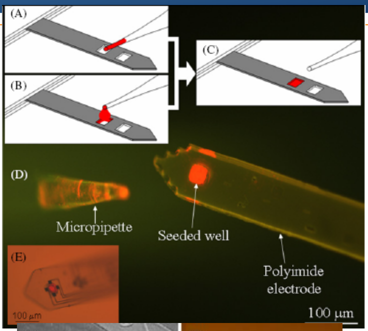


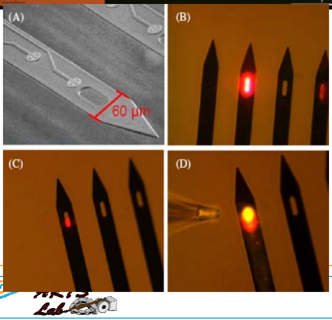
He and Bellamkonda, Biomaterials 2005



The combined use of polyethyleneimine (PEI) and laminin (LN) allows to achieve a better neuronal adhesion

Micro-wells and drug delivery





- Hydrogels infused with bioactive molecules are deposited within wells in the substrate of the device
- This method allows local drug delivery without increasing the footprint of the device
- In addition, each well can be loaded individually, allowing spatial and temporal control
- In vivo testing verified the following: diffusion of the bioactive molecules, integration of the bioactive molecules with the intended neural target and concurrent extracellular recording using nearby electrodes

Williams et al., J Neural Eng, 2005

(Nano)Interfaces based on CNT

- Advances in nanotechnology have the potential to interface solid-state electronics with living cells at the subcellular level
- Appropriately configured nanoelectrode arrays (NEAs) should both extract and modulate neural signals more precisely than MEAs, while inducing much less damage to the tissues
-Cabron NanoTubes can be used to this aim designing a new generation of nanointerfaces

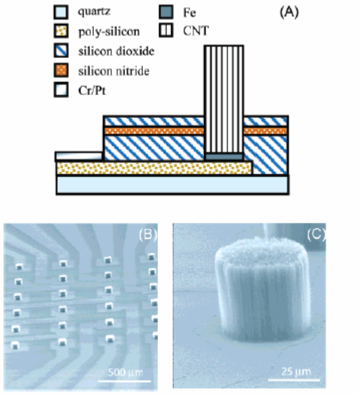


Figure 1. CNT pillar microelectrodes: (A) schematic of the cross section (not to scale); (B) a 6 × 6 array of 30 μm × 30 μm electrodes; (C) a 50 μm diameter electrode.

Wang et al., 2006
Nguyen-Vu et al., 2006

Nanowires

- ☐ A structure that is both sufficiently stiff for cortical penetration and sufficiently fine to meet the sub-cellular criterion has not yet been developed
- ☐ A conventional backbone or shank geometry, but with an adjoining lattice structure has been developed
- ☐ This design could provide a new tool to investigate the tissue response in the central nervous system and may rovide improved chronic recordings

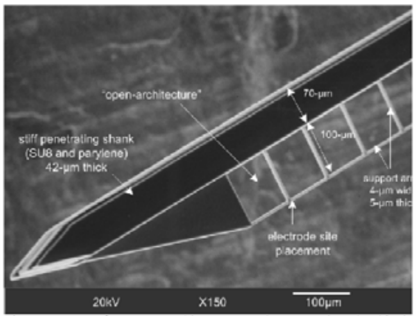


Fig. 1. SEM of an open-architecture parylene neural probe (tip is shown). The primary design principle is to move the electrical/chemical sensing site to the lateral edge of a fine lattice structure where cellular encapsulation is expected to be less dense. A critical parameter is the support arm dimensions and in this case is 4-µm by 5-µm.

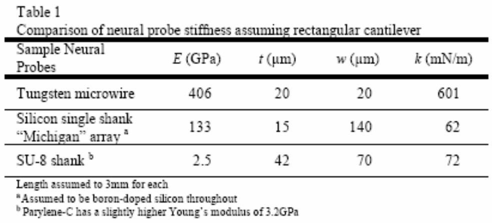


Table 1
Comparison of neural probe stiffness assuming rectangular cantilever

Sample Neural Probes	*E* (GPa)	*t* (µm)	*w* (µm)	*k* (mN/m)
Tungsten microwire	406	20	20	601
Silicon single shank "Michigan" array [a]	133	15	140	62
SU-8 shank [b]	2.5	42	70	72

Length assumed to 3mm for each
[a] Assumed to be boron-doped silicon throughout
[b] Parylene-C has a slightly higher Young's modulus of 3.2GPa

Seymour and Kipke, Proc EMBC, 2006

Cortical interfaces - Summary

- ☐ Cortical neural interfaces are becoming more and more **smart microdevices** embedding different advanced subsystems
- ☐ The aim is to have stable recordings during long-term chronic experiments
- ☐ This result will be very important for neuroscience (e.g., analysis of cortical modifications during learning) and to develop hybrid bionic systems

Intraspinal electrodes

- Neural interfaces can be also used to stimulate the spinal cord to restore function in quadriplegic and paraplegic subjects

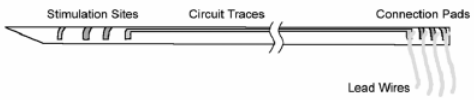


Fig. 1. Electrode design. Circuit traces run down the shaft to link eac connection pad to one stimulation site. Lead wires are bonded to the connectio pads. The electrode components are not to scale.

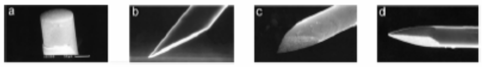
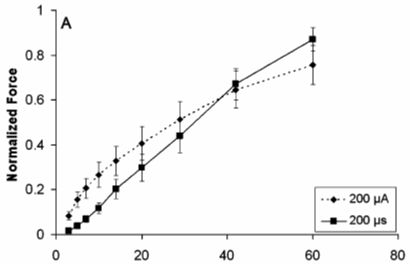


Fig. 2. Four tip styles tested for insertion forces: (a) blunt, (b) slant, (c) chisel, and (d) hypo. All fibers were 70 μm in diameter once the 7.5-μm-thick polyimide coating was ablated.



Snow et al., IEEE T-BME 2006

Scaffolds for spinal cord regeneration

- A multiple-channel, biodegradable scaffold
- Poly(lactic-co-glycolic acid) (PLGA) with co-polymer ratio 85:15 was used

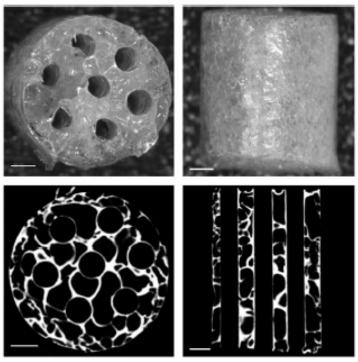


Fig. 2. PLGA scaffolds created from parallel wire molds. Top panels: photographs, and bottom panels: µCT slices. Left: cross-sectional view, and right: longitudinal view. Each scale bar = 500 µm.

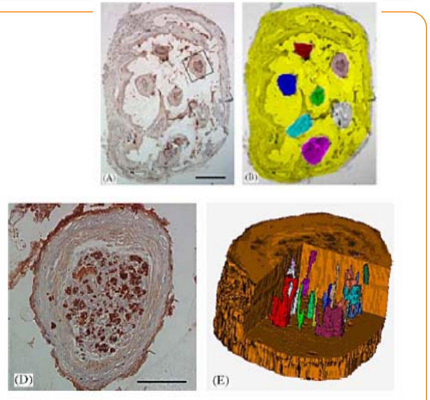


Fig. 8. Histological images of tissue cables within scaffold channels. (A) Histological cross section near rostral end of scaffold showing tissue cables within all seven channels; bar = 500 µm and applies to both A and B. Boxed region is shown in greater detail in D. (B) Histological cross section shown in A with channels segmented and displayed in color. (C) Orthographic, wedged view of 16 serial slices registered, segmented, and reconstructed to reveal 3-D structure of channels. (D) Histological cross section of boxed region in A; scale bar = 100 µm. (E) Orthographic, wedged view of reconstructed channel shown in D, with segmented axon bundles displayed in color.

Moore et al., Biomaterials, 2006

Outline of the talk

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☐ Neural interfaces with the peripheral nervous system

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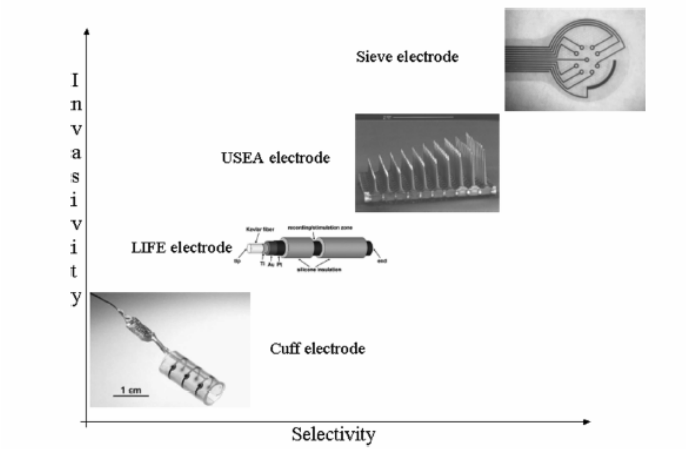
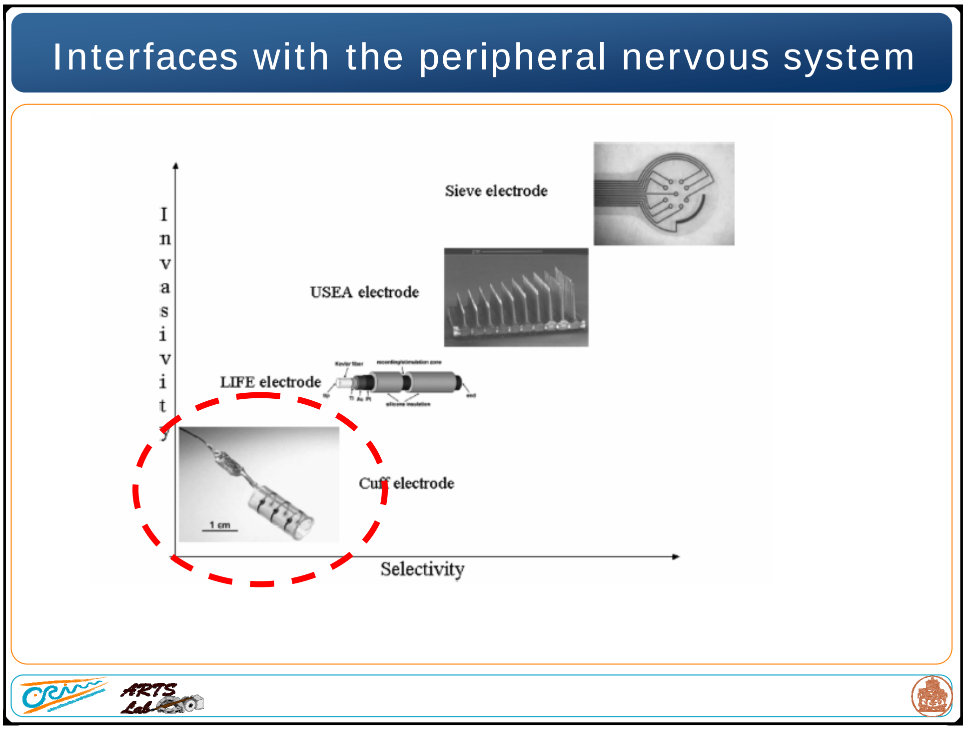
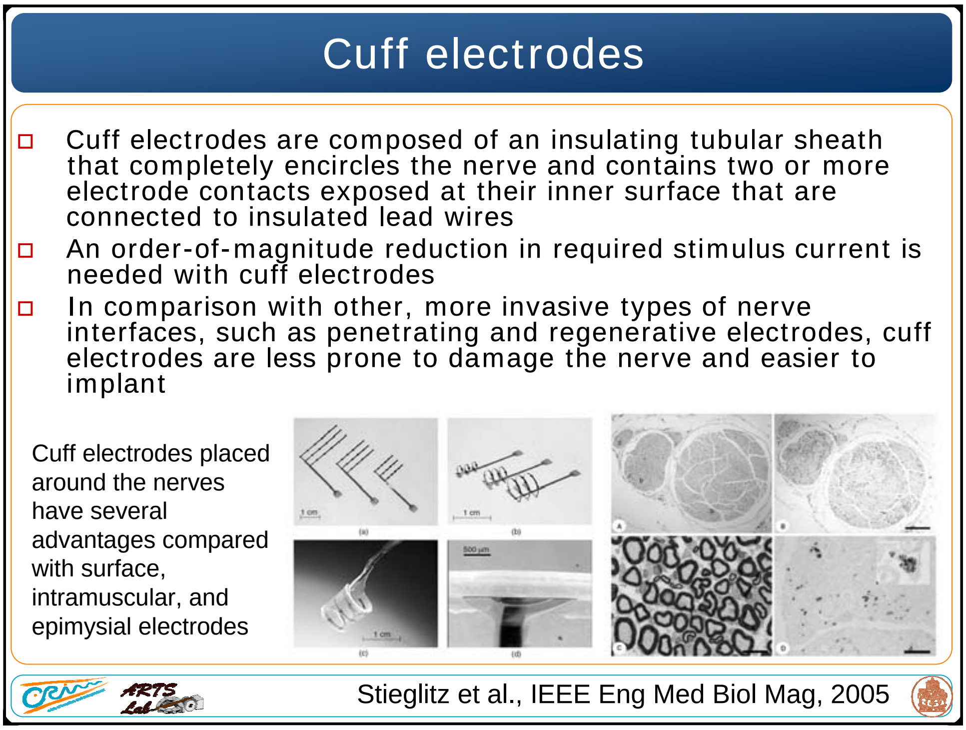
Interfaces with the peripheral nervous system



Navarro, Micera, Dario, et al., JPNS, 2005



Interfaces with the peripheral nervous system

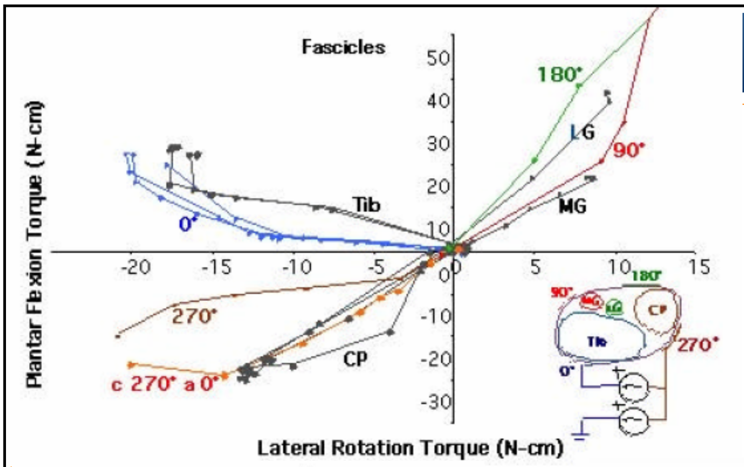


Cuff electrodes

- ☐ Cuff electrodes are composed of an insulating tubular sheath that completely encircles the nerve and contains two or more electrode contacts exposed at their inner surface that are connected to insulated lead wires
- ☐ An order-of-magnitude reduction in required stimulus current is needed with cuff electrodes
- ☐ In comparison with other, more invasive types of nerve interfaces, such as penetrating and regenerative electrodes, cuff electrodes are less prone to damage the nerve and easier to implant

Cuff electrodes placed around the nerves have several advantages compared with surface, intramuscular, and epimysial electrodes

Stieglitz et al., IEEE Eng Med Biol Mag, 2005



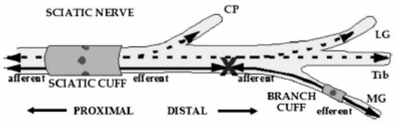


Fig. 1. Full and selective activation of an individual nerve branch was tested by using a branch cuff on the corresponding nerve branch (the MG in this example). The branch cuff was used to activate the branch nerve completely. Activation of nerve fibers serving that nerve branch, by stimulation applied to the sciatic cuff, will not change the resulting output since the branch cuff has already activated those fibers (solid lines). Activation of nerve fibers serving other nerve branches, by stimulation applied to the sciatic cuff, will propagate to different muscles and, therefore, cause a change in the resulting output (dashed lines).

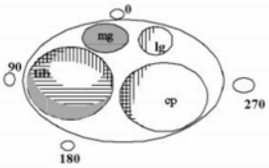
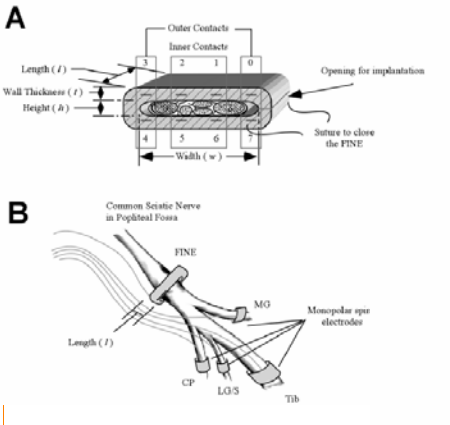
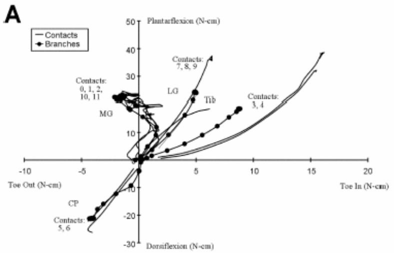
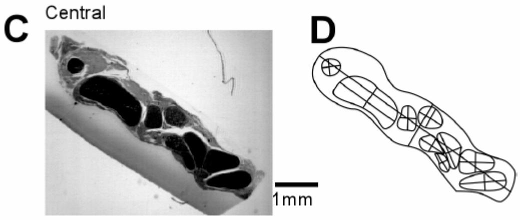


Fig. 21. Schematic representation of cat sciatic nerve containing four motor fascicles, tibial (tib), medial gastrocnemius (mg), lateral gastrocnemius (lg) and common peroneal (cp). Electrode contacts in the self-sizing spiral cuff electrode are labeled 0°, 90°, 180°, and 270°. Grayed areas represent axon populations activated when stimuli (c180°a90°) and (c0°) are separately applied. The vertically hatched areas depict axons stimulated to subthreshold levels by (c0°), and horizontal hatched areas depict axons stimulated to subthreshold levels by stimuli (c180°a90°). Regions where the two subthreshold regions overlap to create suprathreshold excitation have overlapping horizontal and vertical hatched areas.

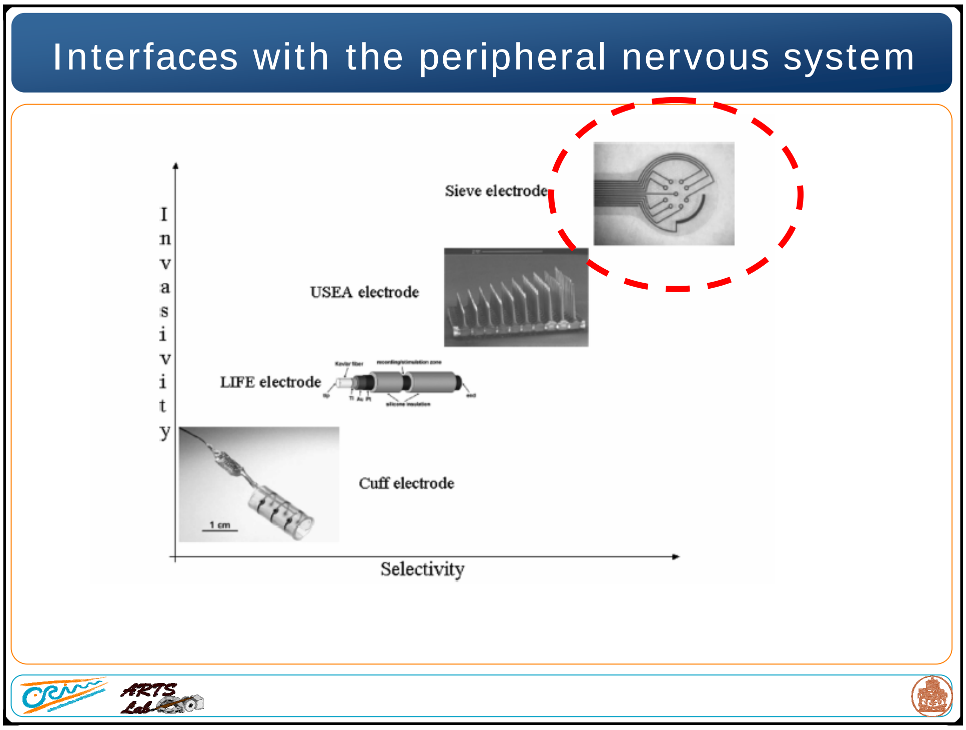
FINE electrodes







Yoo, Sahin, Durand,
Ann Biomed Eng, 2004



Interfaces with the peripheral nervous system

Invasivity

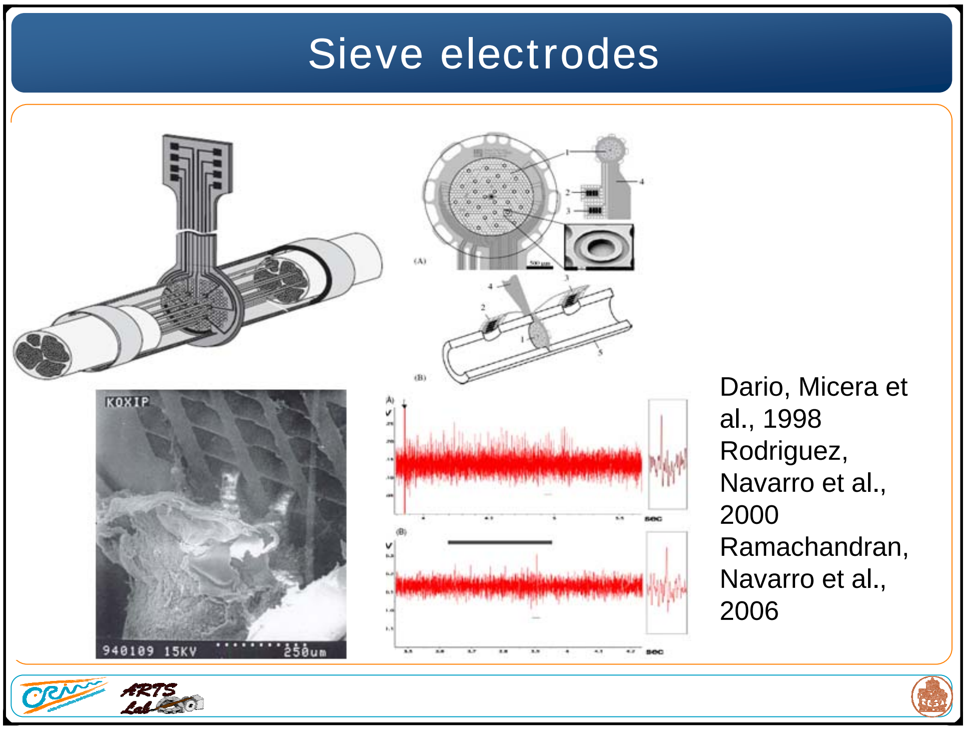
Sieve electrode

USEA electrode

LIFE electrode

Cuff electrode

Selectivity



Sieve electrodes

Dario, Micera et al., 1998
Rodriguez, Navarro et al., 2000
Ramachandran, Navarro et al., 2006

Sieve electrodes

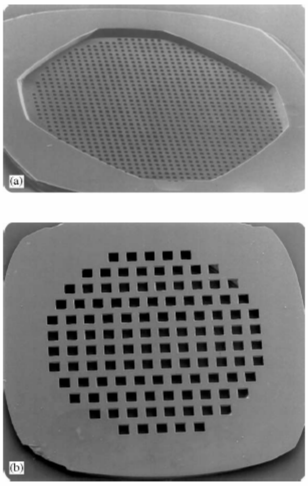


Fig. 2. SEM of fabricated 30 or 90 μm sieve electrodes. Rear ((a) 30 μm — 20%) and front side ((b) 90 μm — 20%) of the sieve electrodes processed according to the scheme depicted in Fig. 1.

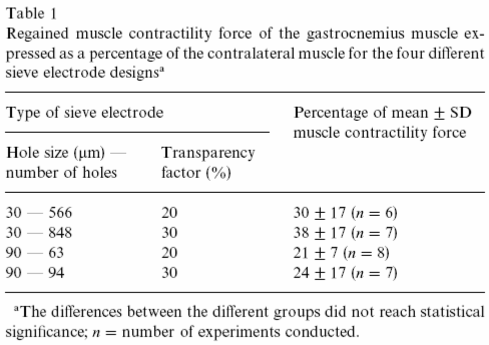


Table 1
Regained muscle contractility force of the gastrocnemius muscle expressed as a percentage of the contralateral muscle for the four different sieve electrode designs[a]

Type of sieve electrode		Percentage of mean ± SD muscle contractility force
Hole size (μm) — number of holes	Transparency factor (%)	
30 — 566	20	30 ± 17 ($n = 6$)
30 — 848	30	38 ± 17 ($n = 7$)
90 — 63	20	21 ± 7 ($n = 8$)
90 — 94	30	24 ± 17 ($n = 7$)

[a] The differences between the different groups did not reach statistical significance; n = number of experiments conducted.

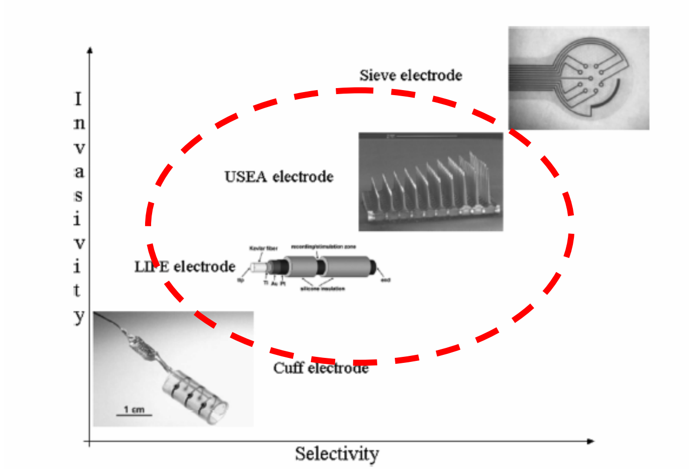
Wallman et al., Biomaterials, 2001

Evaluation of long-term nerve regeneration through regeneration type electrodes

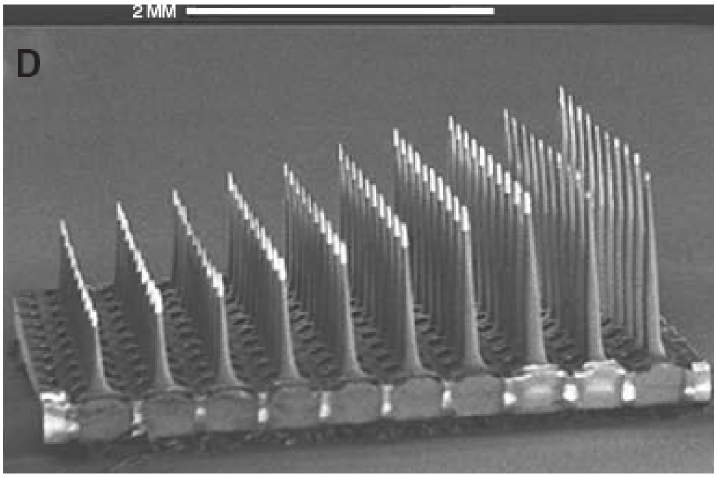
- Polyimide sieve electrodes implanted in the rat sciatic nerve allowed regeneration of axons through the array of via holes in all animals implanted
- With increasing implantation time from 2 to 6 months there was increasing number and progressive maturation of regenerated axons
- In some rats compressive axonopathy progressed at 6 to 12 months, causing loss of regenerated fibers and decline in target reinnervation
- Regeneration was limited in comparison with nerves repaired with a silicone guide without sieve electrode (obstacle to regeneration)
- Maintenance of regenerated axons is difficult in the absence of distal targets organs, as in amputed limbs

Lago, Navarro et al. Biomaterials 2005

Interfaces with the peripheral nervous system

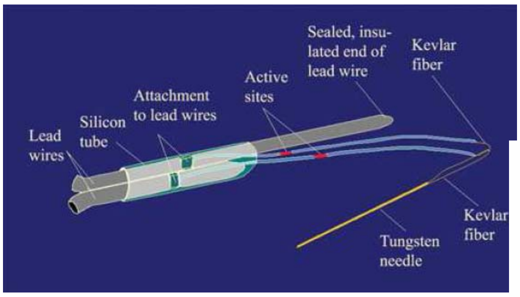


Slanted “Utah” array



McDonnall, Clark, and Normann, IEEE T-NSRE, 2004

Longitudinal Intra-Fascicular Electrode (LIFE)



Yoshida et al., 1999

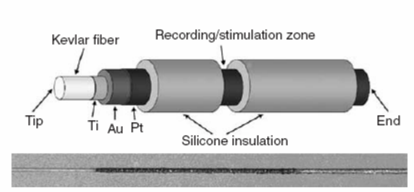
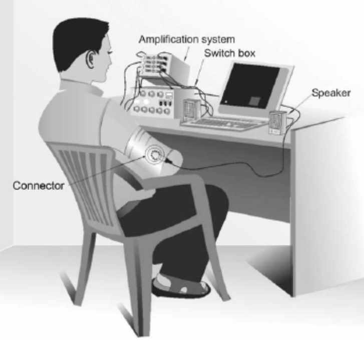


Figure 10. Schematic representation of a polymer-based intrafascicular electrode (polyLIFE). The polyLIFE consists of a Kevlar® fiber, metallized with titanium (Ti), gold (Au), and platinum (Pt) and insulated with silicone. The recording/stimulation zone consists of approximately 1 mm non-insulated portion of the metallized fiber. At the bottom panel, micrograph of the recording/stimulating zone of a LIFE made from metallized Kevlar fiber. In the center is the recording/stimulating region where platinum black has been deposited *(from Lawrence et al., 2003; McNaughton and Horch, 1996, with permission).*

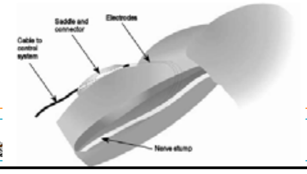
Intraneural electrodes seem to represent a good trade-off between high selectivity and reduced invasivity

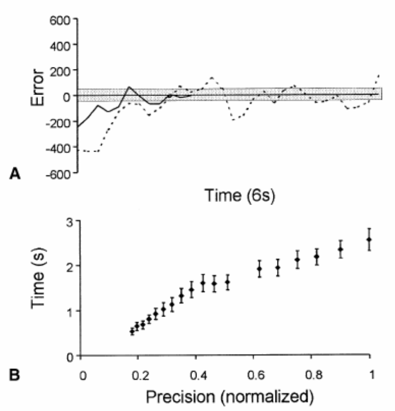
Lawrence et al., 2003

LIFEs for the bi-directional control of hand prostheses



Horch and colleagues (J Hand Surg 2004, J Neurophysiol 2005) recently implanted LIFEs in 8 amputees for acute experiments

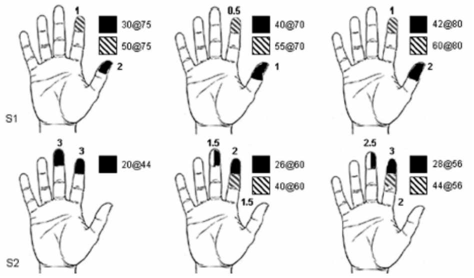




Volitional control of motor activity recorded with LIFEs. (A) Cursor position, controlled by the rate of production of action potentials recorded from a LIFE; (B) The more precisely the cursor was positioned the longer it took to achieve that level of precision

LIFEs for sensory feedback

•Electrical stimulation (modulation of stimulus frequency and amplitude) were performed through one or more of the implanted LIFEs



(Dhillon, Horch et al J Neurophysiol 2005)

- Stable unimodal distally elicited sensations of touch and/or proprioception localized to the digits in the majority (70%) of the cases
- Amputees reported either movement of a given finger joint or movement of the entire digit (proprioceptive sensations) and reliably distinguish different degrees of joint flexion - two subjects consistently reported a referred sensation of phantom grip opening and closing

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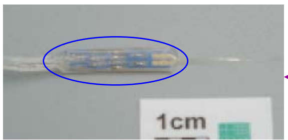
Bidirectional control of an artificial prosthesis

Efferent Control

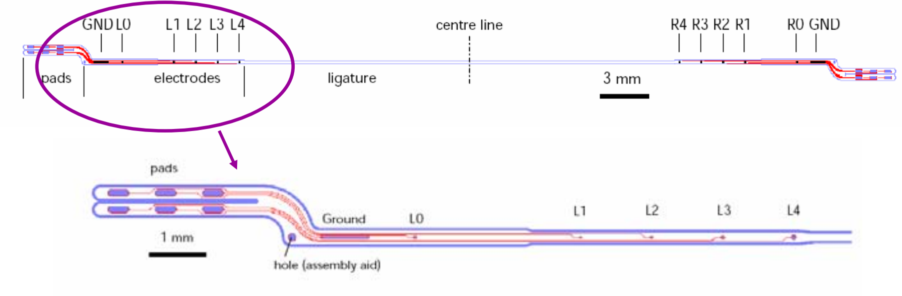
Sensory Feedback

Dhillon, Horch et al J Neurophysiol 2005

Thin-film LIFEs



The active part of the electrode is made of a flexible polyamide thin-film 5µm thick. The polyimide acts as substrate and as insulation on which platinum tracks are sputtered



- L1-L4 and R1-R4 are electrode contacts on the left and right part of the device respectively.
- L0 and R0 are the indifferent recording reference electrodes.
- Two large ground electrodes are placed at the end of the electrode area needed for tripolar recording.

Koch, Hoffmann, et al., Fraunhofer Inst. Biomed. Eng.

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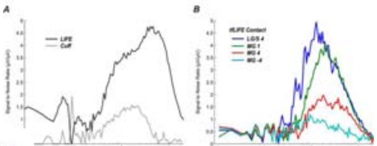
tf-LIFE ADVANTAGES

- ➢ The flexibility of the innovative electrode reduces relative drifts with nerve fascicules
- ➢ It interfaces more axons with one insertion
- ➢ The large number of active sites enhances the signal-to-noise ratio
- ➢ Signals coming from more than one nerve fiber can be discriminated
- ➢ The increase selectivity can allow to deliver a more effective sensory feedback

ENG signals recorded with tf-LIFEs



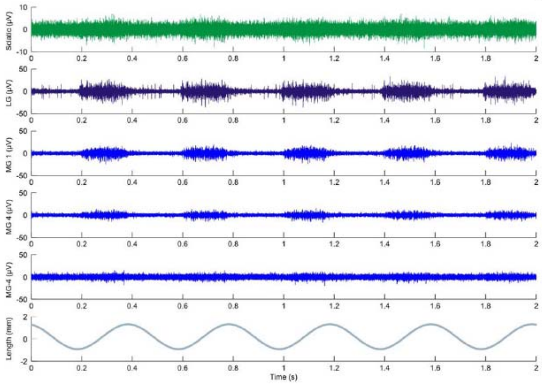


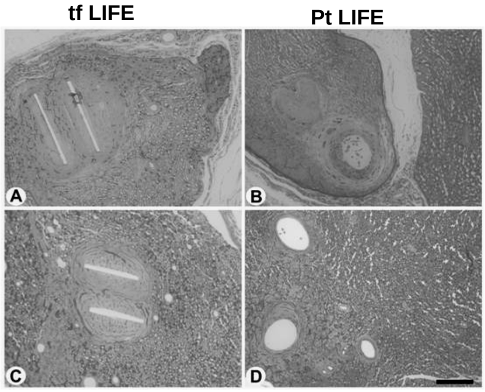
Figure 3 Simultaneously recorded activity from electrodes implanted in branches of the sciatic nerve in rabbit. The top trace is the activity recorded from the cuff electrode. The second trace is from one site of a tfLIFE implanted in the LG/S nerve. The next three are three sites of a tfLIFE implanted in the MG nerve. The final trace is a record of the length of the muscle. The muscle afferents can be seen to be responding to the lengthening phase of the muscle length. The neural signals were bandpass filtered for this figure (300Hz – 10kHz).

Acute experiments in rabbits

Prof. Ken Yoshida

Aalborg University (DK)

Tf-LIFE – Histology



Peroneal nerve

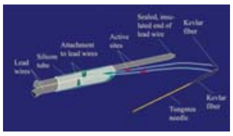
Tibial nerve

Bar = 100 µm

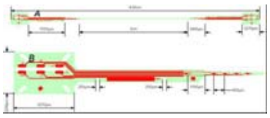
- Wholes created by the LIFE
- Fibrous cover around the electrode sites.
- In B the opening created by the Pt wire is partially occupied by tissue during sample processing.

Lago, Navarro et al., 2006

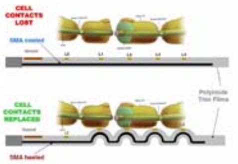
Evolution of LIFE electrodes



First generation
LIFEs using Pt



Second generation
Thin film LIFEs



Third generation
Actuation of tfLIFEs
Biomechanical characterization
Advanced signal processing techniques

Interfaces with the PNS - Summary

- Cuff electrodes seem to be quite robusts. They seem to be a good solution to develop FNS-based systems to restore function in SCI subjects
- Intra-neural PNS interfaces seem to be a good solution in the short term to implant in amputees a cybernetic hand prostheses
- Sieve interfaces are potentially very interesting because they could allow a more selective stimulation/recording increasing the quality/quantity of sensory feedback and the number of controllable degrees of freedom

Conclusions

- In the recent past several approaches have been used to develop more effective neural interfaces
- They are becoming more and more complex **smart microdevices** embedding several features
- Many efforts are still necessary to define interfaces able to record during long-term chronic experiments
- This is crucial for both neuroscientific and robotic applications

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Thanks for the attention!!

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