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Flexible implantable thin film neural electrodes

Sami Myllymaa, Katja Myllymaa and Reijo Lappalainen
University of Kuopio, Department of Physics
Finland

1. Introduction

Implantable neural electrodes are widely used tools in basic neuroscience to study the behavior and function of the central nervous system at the tissue and cellular level. There is also a growing interest in the clinical applications of stimulating and recording neural electrodes as well as implantable neural prostheses in which the microelectrodes act as a functional element that connects neurons, i.e. the electrically active cells of the nervous system to the electronic circuitry. Several implantable neural prostheses such as cardiac pacemakers, cochlear implants and deep brain stimulators have been already successfully commercialized. Cochlear implant is a surgically implanted electronic device that utilizes an electrode array inserted into the scala tympani of the cochlea to stimulate the auditory nerve through the bone, enabling the deaf to hear sounds. Deep brain stimulators consist of intracortically implanted electrodes through which a high frequency electrical stimulation is delivered to a targeted region of the brain; they are used in treating several neurological disorders, e.g. Parkinson's disease. Intracranial electrodes consisting of depth electrodes (probes) and subdural electrodes are used to measure local field potentials and occasionally spikes in some clinical cases such as in the presurgical evaluation of patients who are candidates for epilepsy or brain tumor surgery.

Despite the major advances in microsystem technologies and microelectronics, most human neural electrodes are handcrafted from platinum foils and silicone sheet and therefore the devices are quite bulky. Miniaturized electrode arrays with high-channel densities are common in animal models, but their human counterparts are mainly being investigated or at best undergoing clinical trials. Microfabrication techniques, e.g. photolithography and thin film deposition could be useful to obtain multichannel microelectrodes with a high channel density. This would result in a higher spatial resolution which is necessary for accurate recording and stimulation of tiny nervous structures. One major advantage of using well-proven lithographic and thin films techniques is the high reproducibility and the possibility to manufacture many electrodes in a single batch. Additionally modern nanotechnology provides many tools and opportunities to improve the long-term functionality and biocompatibility of implantable electrodes. These include the use of surface modifying thin films of high purity materials and controlled nanotopography and/or microtopography which can be achieved for example by laser ablation techniques.

In this chapter, we provide a description of requirements related to implantable electrode materials. And then we discuss the state of the art of the electrodes used in intracranial

recordings and stimulation, taking into account not only neurophysiological research but also their clinical applications. We will depict the fabrication process and performance of our flexible polyimide-based microelectrodes as a tool for multi-channel cortical surface recordings. We critically review the corresponding other flexible sensor approaches and compare our fabrication methods, material choices and *in vivo* and *in vitro* performance of our electrodes to those of other research groups. We will also discuss the future trends and strategies to prolong functional life span and to minimize the immune response to implanted electrodes.

2. Requirements for materials used in implantable electrodes

The requirements and demands placed on the materials used in invasive neural electrodes and prostheses are understandingly very high. There are a number of important factors that must be taken into account when selecting materials for electrodes and for the substrate/encapsulation layer to ensure optimal performance and longevity of the neural implant. The ideal neural implant material must be biocompatible without triggering any vigorous local or generalized host response or allergic reactions. The electrode-tissue impedance must be stable and low enough to enable long-term reliable measurements/stimulations. Additionally, the materials should be compatible with magnetic resonance imaging and they should be visible radiographically (Geddes & Roeder, 2003). In this section, we will discuss these requirements by describing materials typically used particularly concentrating on their electrochemical properties. Biocompatibility aspects will be discussed in section 5.

2.1 Electrode materials

The key function of recording electrodes is to convert the ionic current around the electrode site into electron current. On the other hand, stimulation electrodes deliver the electrical charge to brain tissue aiming to stimulate excitable cells and tissue. Electrodes can be roughly divided into polarizable and non-polarizable electrodes. Ideally polarizable electrode passes current from the electrode to an electrolytic solution by changing the charge distribution within the solution near the electrode. This kind of electrode acts like a capacitor, and only the displacement current crosses the interface. In contrast, ideally a non-polarizable electrode allows the current to pass freely through the electrode-electrolytic interface without changing the charge distribution in the electrolytic solution.

Two identical bioelectrodes in contact with electrolyte can be modeled in an equivalent circuit model as presented in Fig. 1A. Electrode polarization impedance consists of Warburg (polarization) resistance R_w and capacitance C_w. The Faradic resistance, R_f as a parallel with Warburg components, provides a route for direct current to pass through the interface. R_s is the resistance of the electrolyte solution. Polarization reactance ($X_w = 1/2\pi fC_w$) as well as R_w are both frequency dependent: they decrease as ($1/\sqrt{f}$) with increasing frequency. At a sufficient high frequency, the impedance between two electrodes in saline asymptotically approaches the value of R_s (Fig. 1B). R_w, C_w and R_f are also dependent on the geometry of the electrode material, electrode size and current density.

A silver-silver chloride electrode (Ag/AgCl) is almost perfectly non-polarizable, has a small and stable offset potential and therefore is widely utilized as the surface (skin) biopotential electrode, but it cannot be used as an implantable electrode because of the rapid dissolution

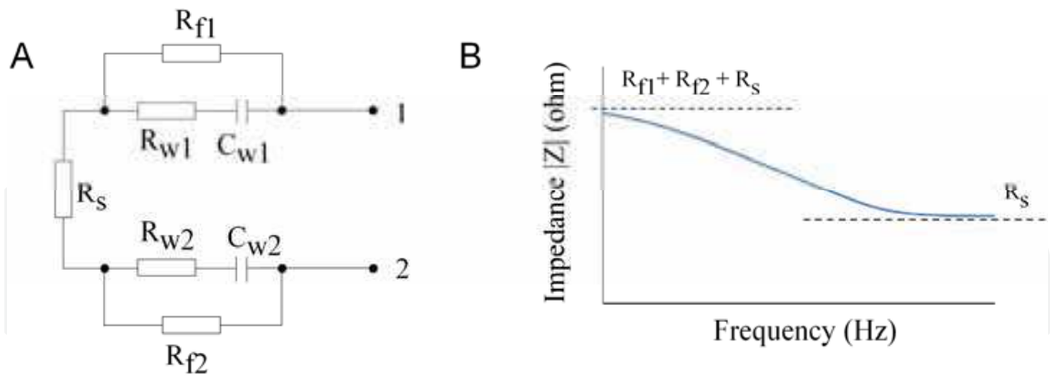


Fig. 1. (A) The equivalent circuit model for a two identical bioelectrodes immersed in saline. (B) Typical electrode-electrolyte impedance graph measured between the terminals 1 and 2 as a function of frequency

of silver. Furthermore, AgCl as well as pure Ag has a toxic effect on neural tissue (Yuen et al., 1987). Noble metals such as platinum (Pt), gold (Au) and iridium (Ir) have been the most commonly used electrode materials in neural prosthetic applications due to their excellent corrosion resistance and biocompatibility properties (Geddes & Roeder, 2003). They are highly polarizable electrodes meaning that the ionic current in tissue can give rise to an electric current in the metal electrode, and almost no charge carriers pass through the interface. Current densities for recording purposes are so low that the interface has a linear current-voltage relationship. If one wishes stimulation, then higher current densities are required to elicit neural excitation reactions resulting in Faradaic current flow, in which charge carriers pass through the interface. Irreversible electrochemical reactions can occur and change the chemical composition of the electrode-electrolyte interface. The limit for a maximum reversible charge injection depends on the electrode material as well as its shape, size and the stimulation waveform.

Pt is clinically utilized as an electrode material in various neural applications such as in cardiac pacemakers, cochlear implants and subdural strip and grid electrodes. Pt suffers from corrosion only slightly in both recording and stimulating use. Pt is commonly used as an inert reference electrode in electrochemistry since it is at the extreme of the galvanic series. Au is often used in recording electrodes but it suffers from corrosion if used for stimulating purposes. On the contrary, Ir is mainly utilized as a stimulating electrode. The electrode properties of Ir can be further developed by electrochemical activation that leads to the adhesion of a porous and very stable oxide layer on the electrode surface. The property of enhanced corrosion resistance of activated iridium oxide (AIROF) is particularly important in stimulating electrodes to avoid metal dissolution during electric pulsing. The AIROF has a high charge delivery capacity and therefore it is well suited for use in stimulating electrodes. Activation also reduces the electrode impedance due to the porosity. Another new potential electrode candidate for use in stimulating electrodes is titanium nitride (TiN). The high charge delivery capacity of TiN is based on its high effective surface area due to the columnar structure of this material. TiN is already being clinically utilized in pacemakers. Optically transparent indium tin oxide (ITO) is an extensively employed electrode material used in electrochemistry, but at present its use in neurophysiology is virtually limited to *in vitro* microelectrode arrays for recording electrical signals from

neurons. The compatibility of ITO for chronic *in vivo* recording is not completely understood although recent investigations have shown promising results in terms of cell adhesion and proliferation (Bogner et al., 2006) as well as protein adsorption (Selvakumaran et al., 2008). Correspondingly, the electrically conductive hard ceramic, glassy carbon is an extensively applied electrode material in electroanalytical chemistry, but it is rarely used as an implantable electrode.

2.2 Substrate and encapsulation materials

The substrate and encapsulation materials need to be biocompatible, biostable and possess good dielectric properties. Good biocompatibility means that material must not evoke a toxic, allergic or immunologic reaction. Biostability means that the implant material must not be susceptible to attack by biological fluids or any metabolic substances. The surface area of substrate/encapsulation material is much larger compared to areas of the active electrode sites. Therefore substrate and insulator materials have an important role in long-term stability and functioning of neural implants.

A substrate material that has been widely utilized for neural interfaces in the central nervous system is silicon (Si). Silicon dioxide (SiO_2) and silicon nitride (Si_3N_4) are typical insulators used with silicon base. However, there is a mismatch between the mechanical properties of the soft brain tissue and the rigid silicon and thus causes many adverse effects such as tissue damage, inflammatory reactions and scar formation (Polikov et al., 2005). Therefore, there has been a growing interest toward developing polymer-based implant materials that could be flexible enough to mimic biological tissue and to reduce mechanical damage but not evoking any adverse tissue reactions. Additionally, their composition and surface properties can be modified in a variety of ways to make by them more biocompatible. Polymers can be employed as both substrate and/or encapsulation materials. Different flexible polymer materials such as polyimide, benzocyclobutene (BCB), polydimethylsiloxane (PDMS), parylene and epoxy resins have been recently investigated as substrate/encapsulating materials in implantable neural interfaces (Cheung, 2007). Polyimide has been used as an insulator in microelectronics because of its numerous excellent properties: excellent resistance to solvents, strong adhesion to metals and metal oxides and good dielectric properties. The volume resistivity and dielectric strength of polyimide are comparable to silicon and typical silicon insulation materials, such as SiO_2 and Si_3N_4 (Stieglitz et al., 2000). When used as a neural implant material, polyimide has also appropriate mechanical properties and its biocompatibility has been demonstrated in many studies *in vitro* and *in vivo* (Stieglitz et al., 2000; Richardson et al., 1993). Table 1 summarizes some important properties of polyimide and PDMS in comparison to Si and SiO_2. The major disadvantage of polyimide is its permeability to environmental moisture and ions that could be crucial in terms of short circuiting and reducing the electrode's life span. BCB has been a widely used material in microelectronics due to its low moisture absorption, good dielectric properties and chemical stability. Recently BCB has been demonstrated to be a potential material for use in implantable neural interfaces (Lee et al., 2004a). Parylene and silicone rubber (PDMS) are known to be biocompatible materials and they are approved for use as an implanted material in medical devices (i.e. FDA approved). Parylene is a thermoplastic polymer that can be vapor-deposited at room temperature to form pin-hole free barrier coatings that are stress-free, chemically and biologically inert and stable as well as being

minimally permeable to moisture. Paralyne as well as PDMS are both hydrophobic and optically transparent materials and thus they can be used in optical elements.

	Units	PDMS	Polyimide	Silicon	Silicon dioxide
Tensile strength	kg/mm^2	0.4-1.1	13.5	1225	5-14
Elongation	%	140	15	-	-
Density	g/cm^3	1.11	1.45	2.1	2.3
Young's modulus	kg/mm^2	0.04 – 0.09	245	$20 \cdot 10^3$	$7 \cdot 10^3$
Dielectric constant at 1 kHz, 50 % RH	relative (ε_r)	2.70	3.3	12	3.9
Dielectric strength at 1 KHz, 50 % RH	V/cm	$1.4 \cdot 10^5$	$2 \cdot 10^6$	$3 \cdot 10^5$	$6 \cdot 10^6$
Volume resistivity	$\Omega \cdot cm$	$2.9 \cdot 10^{14}$	10^{16}	-	10^{16}

Table 1. Some physical properties of PDMS (Sylgard 184, Dow Corning Inc.) and polyimide (Pyralin PI 2525, HD Microsystems GmbH) in comparison to silicon and silicon dioxide. Values are taken from the datasheets for Sylgard 184 (Dow Corning Inc.) and for Pyralin PI 2525 (HD Microsystems GmbH) and from Stieglitz et al., 2000; Mata et al., 2005; Armani et al., 1999

3. Recent recording and stimulating brain electrodes in clinical use

Human electroencephalography (EEG) recordings are typically performed with different numbers of electrodes attached to the scalp and measuring the potential differences between electrodes. However, source localization of scalp-EEG is rather poor. To achieve better spatial resolution, it is advantageous to place the electrodes closer to the brain tissue. Both penetrating (intracortical) electrode probes and non-penetrating electrode arrays placed on the surface of cerebellum cortex have been utilized to measure neuronal action potentials and local field potentials from the brain. Compared to human scalp-EEG, intracranial recordings are advantageous in terms of increased spatial resolution, signal amplitude level and reduced noise level meaning that one can acquire more detailed maps directly of brain. However, the use of penetrating electrode probes in humans is limited to the areas destined for surgical resection because of the risk of damaging the brain tissue, whereas flexible subdural strip and grid electrodes placed on the surface of cortex are used as a less invasive method in some clinical cases, e.g. in mapping cerebellum cortex in patients undergoing epilepsy or brain tumor surgery. The signals recorded with subdural electrodes are considerably higher in amplitude because they are much closer to the source of the activity, and are separated from it by only a relatively high conductivity media (CSF, brain parenchyma). Subdural electrodes are virtually free of artifacts (e.g. not affected by electrical signals originating from muscles) that are seen in scalp-EEG, and thus they yield a much higher signal-to-noise ratio (Nair et al., 2008). Typical commercially available subdural strip and grid electrodes consist of stainless steel or platinum foil contacts with exposed diameter of about 2-3 mm embedded in flexible biomedical-grade silicone plates (e.g., AD Tech

Medical Instrument Corp., Racine, WI, USA; PMT Corp. Chanhassen, MN, USA). Epidurally implanted surface electrodes as well as penetrating intracortical probes are also utilized for stimulating purposes in humans. Motor cortex stimulation (MCS) is a relative new technique in which surface electrodes are used at low current densities to stimulate the motor area (Brodman 4) in treating chronic neuropathic pain (Rasche et al., 2006). Deep brain stimulators consist of intracortically implanted electrodes through which a high frequency electrical stimulation is delivered to targeted regions of the brain, for example being used in treating severe neurological disorders, e.g. in Parkinson's disease.
Although modern microfabrication techniques possess a great potential to develop novel high-density microelectrode arrays for recording of brain activity or electrical stimulation of neural tissue, and these kinds of microarrays are extensively utilized in animal studies, no microelectrode array suitable for use with human patients is on the market today. For example, different lithographic and thin film techniques could be utilized in the development of substrate-integrated electrodes with higher spatial resolution than the present subdural electrodes in clinical use.

4. Microelectrode arrays in animal models

Neurophysiologists have traditionally performed chronic cortical recordings in animal models with insulated microwires and wire bundles (Nicolelis et al., 1997; Williams et al., 1999). The first chronic recordings from freely moving animals with stainless steel microwire electrodes were performed in the 1950s (Strumwasser, 1958). The development of photolithographic, silicon etching and thin-film deposition techniques provided novel approaches in the development of improved recording and stimulating systems used in experiments with animal models (Wise, 2005). Silicon has been the most widely used substrate material because of the well-established precise microfabrication methods which have been developed for integrated circuits. The main advantage of microfabricated electrode arrays compared to microwire bundles is the precise control of the electrode sizes and the separations between electrodes. Batch-processing also means that there can be large volume and low-cost production of identical microsensors. Michigan probes (Najafi & Wise, 1986) and Utah arrays (Campbell et al., 1991) are perhaps the best-known Si-based microelectrodes. The typical Michigan arrays are single-shank or multi-shank Si penetrating probes where the electrodes are placed along the length of the shank allowing the measurement of neuronal activity at various depths of the brain tissue. The three-dimensional Utah array consists of 100 conductive Si needles (length 1.5 mm) with platinum coated tips. However, due to mechanical mismatch between the rigid Si (Young's modulus ~ 170 GPa) and soft brain tissue (~3 kPa) and subsequent adverse tissue responses, there has been a growing interest in developing polymer-based implants that could be flexible enough to mimic biological tissue and to reduce adverse tissue reactions.

4.1 Flexible polymer-based microelectrode arrays

Different flexible polymer materials such as polyimide, BCB, PDMS, parylene-C and epoxy resins have been recently investigated as substrate materials in implantable neural interfaces (Cheung, 2007). These polymers are also utilized in coating silicon-based implants providing both a chemical barrier and an electrical insulation layer. The flexibility of the polymer may decrease the mismatch between the mechanical properties of nervous tissue and the rigid

implant and thus reduce the risk of tissue damage and inflammation reactions due to electrode micromotion.

Several polyimide-based microelectrode arrays (MEA), i.e. polyimide-metal-polyimide sandwich structures have been developed in the field of neural engineering for various applications (Cheung, 2007). Typically these approaches utilize polyimide as a base material with a thickness of a few tens of micrometers. A thin film of suitable electrode material, such as Au, Pt or Ir is coated on the top of polyimide by using physical vapour deposition techniques, e.g. sputtering or evaporation, and then they are structured photolithographically. A thin layer (a few micrometers) of insulating material is structured on the top of the metallization layer leaving the desired areas (i.e. electrode sites) open, whereas the interconnecting lines are completely covered to avoid short-circuits in a moist environment containing salt ions. These kinds of flexible microelectrode arrays have been developed for studying brain slices *in vitro* (Boppart et al., 1992), cortical surface field potential recordings (Owens et al., 1995; Hollenberg et al., 2006; Takahashi et al., 2003; Myllymaa et al., 2008b; 2009) and intracortical multiunit neural activity recordings (Rousche et al., 2001; Cheung et al., 2007; Mercanzini et al., 2008) and for action potential recording in nerve and muscle tissues *in vivo* (González & Rodríguez 1997; Rodríguez et al., 2000; Spence et al., 2007). Stieglitz et al. have also fabricated different kinds of polyimide-based microdevices (e.g. sieve and cuff electrodes) for interfacing with regenerating peripheral nerves (Stieglitz et al., 2000; Stieglitz et al., 1997; 2001). Some recently published papers focusing on the development of polymer-based neural microelectrodes for recording brain activity and stimulating the brain tissue are summarized in Table 2.

reference	substrate (S)/ insulator (I) material and their thicknesses	electrode material and its deposition method	electrode size and number of electrodes	electrode impedance measured *in vitro* at 1 kHz	application (performed *in vivo* studies)
Owens et al., 1995	S: polyimide 2 µm I: polyimide 2 µm	evaporated Cr (15 nm) + Au (300 nm) + electroplated Pt black	40 x 40 µm² 24 electrodes (lithographic patterning)	11-16 kΩ	acute evoked potential recording from the surface of ferret cortex
Rousche et al., 2001	S: polyimide 10 µm I: polyimide 10 µm	evaporated Cr (25 nm) + Au (200 nm)	30 x 30 µm² (lithographic patterning)	1837 ± 197.3 kΩ	intracortical recording with bioactive capability
Takahashi et al., 2003	S: polyimide 25 µm I: polyimide < 1 µm	Cr (thin) + Au (200 nm)	80 x 80 µm² 69 electrodes (lithographic patterning)	330 ± 65 kΩ	acute evoked potential recording from the surface of rat cortex
Lee et al., 2004b	S: BCB 10 µm I: BCB 10 µm	Au (200 nm)	20 x 20 µm² 3 electrodes (lithographic patterning)	~1200 kΩ	intracortical recording with micro-fluidic channels

Takeuchi et al., 2005	S: parylene 5 µm I: parylene 5 µm	Au (1 µm)	different geometries and numbers of electrodes	~100 kΩ (single Au electrode inside the channel)	intracortical recording with micro-fluidic channels
Kitzmiller et al., 2006	PDMS	evaporated Pt (200 nm)	200 x 200 µm² 8 electrodes (lithographic patterning)	not mentioned	acute evoked potential recording from the surface of pig cortex
Hollenberg et al., 2006; Yeager et al., 2008	S: polyimide 25/50 µm I: SU-8 epoxy 13 µm	sputtered Ti-W (5 nm) + Au (300 nm)	Ø: 150 µm (round) 64 electrodes (lithographic patterning)	225 ± 90 kΩ	acute and chronic evoked potential recording from the surface of rat cortex
Molina-Luna et al., 2007; Hosp et al., 2008	S: polyimide 7 µm I: polyimide 7 µm	Ti (10 nm) + Au (300 nm) + TiN (800 nm)	Ø: 100 µm (round) 72 electrodes (lithographic patterning)	5-10 kΩ	epidural stimulation mapping of rat motor cortex
Cheung et al., 2007; Mercanzini et al., 2008	S: polyimide 20 µm I: polyimide 1.5 µm + 1.5 µm	sputtered Ti (50 nm) + Pt (200 nm)	Ø: 25 µm (round) 16 electrodes (in two layers)	~1000 kΩ	acute and chronic intracortical recordings into the rat cortex
Myllymaa et al., 2008b; 2009	S: polyimide 30 µm I: polyimide 3 µm	sputtered Ti (20 nm) + Pt (200 nm)	Ø: 100-200 µm (round) 8-16 electrodes (lithographic patterning)	25.5 ± 2.0 kΩ	acute and chronic recording evoked potentials from the surface of rat cortex

Table 2. Microfabricated polymer-based neural electrodes for recording brain activity and stimulating brain tissue (summary of recent publications)

4.2 Development of microelectrode arrays (MEA) for cortical surface recordings

Our sensor research is focused on the development of polymer-based thin film electrodes and electrode arrays which can be used for recording of biosignals as well as for stimulation of excitable tissue. The fabrication and testing of flexible microelectrode array that is suitable for multichannel cortical surface recordings in rats is described in detail elsewhere (Myllymaa et al., 2008b; 2009). Here we discuss the major aspects of the development and fabrication process as well as the results from *in vitro* and *in vivo* testing. The fabrication process was developed and iterated to a fully functional solution during a two year trial period when suitable substrate material, substrate thickness, electrode material, sensor layout and insulation material were optimized (Myllymaa et al., 2008a).

4.2.1 Array fabrication

The fabrication process of the microelectrode array is based on creating magnetron sputter deposited (AJA Inc., Stiletto Serie ST20I), lithographically patterned stable Pt thin films between two biocompatible polyimide layers. The fabrication steps of arrays are schematically illustrated in Fig. 2. The fabrication was implemented on top of microscope glass slides, 2″ x 3″ (Logitech), to guarantee a rigid support during fabrication. As a base layer we used a 25 µm thick Kapton HN film (DuPont) together with spin coated Pyralin PI 2525 (HD Microsystems GmbH) polyimide layer (Fig. 2A). A negative photoresist (ma-N 1420, Micro resist technology GmbH) was spun on the base layer and patterned using 365 nm UV exposure and wet developer chemicals (Fig. 2B). Thin films of Ti (20 nm) and Pt (200 nm) were DC sputtered onto a surface of the base layer (Fig. 2C) and structured with a lift-off technique (Fig. 2D). Ti was used beneath the Pt to improve the adhesion between the polyimide and the metal layer. Then, photosensitive polyimide PI-2771 (HD Microsystems GmbH) was spin coated on an array pattern (Fig. 2E) and patterned with alignment of metallization layer. About a 3 µm thick insulation layer was formed on all positions except for the areas of the electrodes and connection pads (Fig. 2F). Finally, the array was detached from the glass slide (Fig. 2G).

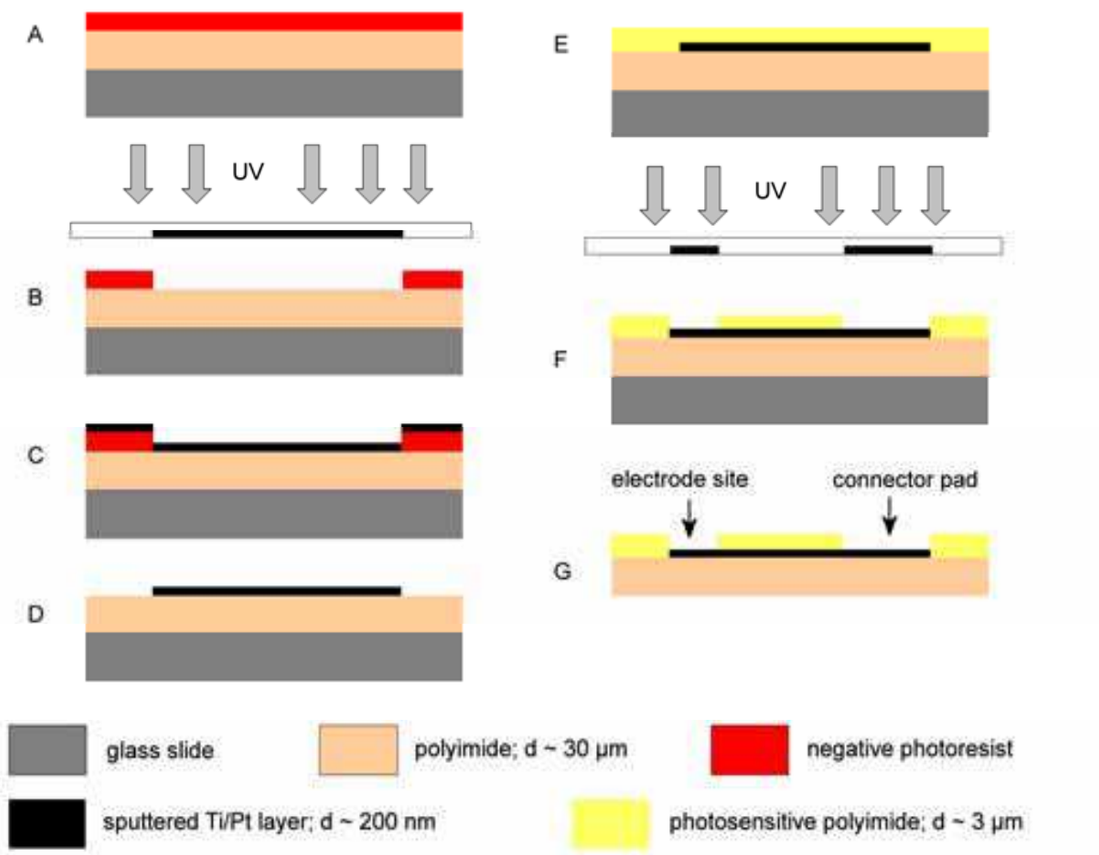


Fig. 2. Fabrication steps of flexible microelectrode arrays. See details in the text

The developed arrays consisted of either 8 or 16 round-shaped Pt-electrodes (round, Ø 100-200 µm) in an area of about 2 mm x 2 mm at the end of polyimide ribbon. Thin film connector pads at one of the edges of polyimide foil were designed to fit into a 16-channel 0.5 mm pitch zero-insertion-force (ZIF) connector (JST Ltd., Halesworth, UK). The ZIF connector was soldered to a thin (0.2 mm) printed circuit board (PCB) adapter. The PCB contains also a 16-channel surface mount microsocket (CLM-serie, Samtec Inc., New Albany, IN, USA) through which the electrical signals from the electrodes are transferred to the preamplifier and further to the recording instrumentation. The prototype of flexible microelectrode array with connector board as well as a schematic view of the array cross-section is shown in Fig. 3.

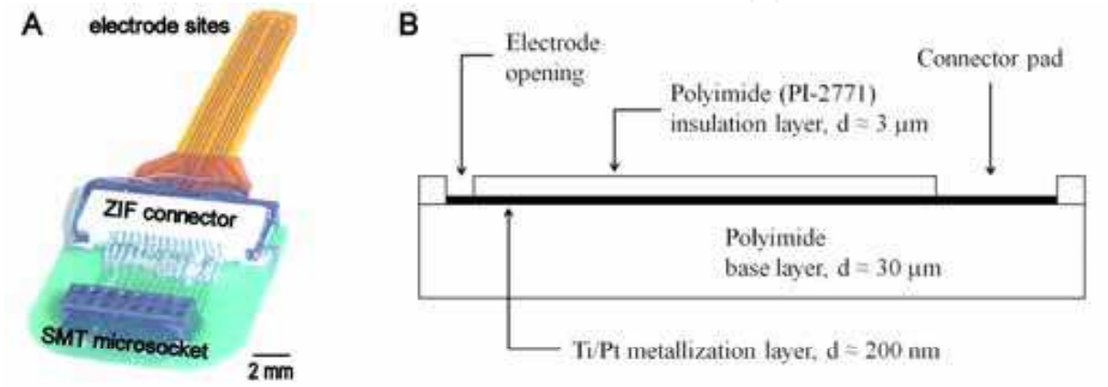


Fig. 3. (A) The developed microelectrode array. The array is connected via a printed circuit board consisting of a ZIF type connector and a SMT microsocket to the recording instrumentation. (B) A schematic illustration of the array cross-section (not to scale, d: thickness)

The use of non-photosensitive polyimide as an insulation layer has been very common in neural interfaces (González & Rodríguez 1997; Cheung et al., 2007; Mercanzini et al., 2008). In contrast, the fabrication process described above utilizes photosensitive polyimide grade that remarkably simplifies the array fabrication i.e. it can be patterned directly by UV exposure and developer chemicals. Thus, no photoresist and/or hard mask as an etch template is needed as is the case with standard non-photosensitive polyimides. Aluminum is a commonly used hard mask material in polyimide dry etching. It is possible that aluminum residuals may remain on the final device after the fabrication process and further come into contact with neural tissue and these ions can be very toxic and cause adverse tissue reactions (Wennberg, 1994). This risk can be eliminated by using photosensitive polyimide. The SEM images (Fig 4) demonstrate that it is possible to pattern the photosensitive polyimide (PI-2771) layer with an almost vertical edge profile without any residuals.

While the excellent biocompatibility of polyimide has been proven in many studies (Richardson et al., 1993; Stieglitz et al., 2000; Seo et al., 2004), these exists only one report focusing on the assessment of cytotoxicy of photosensitive polyimide grade (Sun et al., 2008) involving different chemistry and solvent processes. Therefore, further investigations are

needed to ensure the biocompatibility of photosensitive polyimide grades that there will be no adverse, long term effects and that the material is suitable for chronic implantable use.

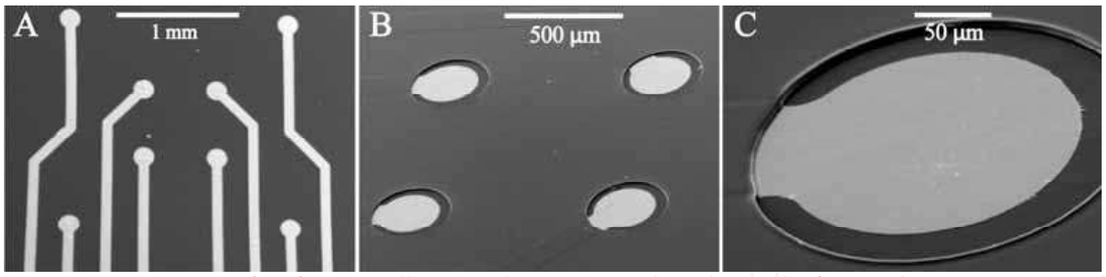


Fig. 4. SEM-image of Ti/Pt metallization layer viewed at the end of recording sites (A) and electrode opening(s) at two magnifications (B-C). A thin insulating layer (photosensitive polyimide) is patterned with alignment of the metallization layer

4.2.2 Electrochemical characterization

Electrochemical impedance spectroscopy (EIS) is a commonly used method to characterize the electrochemical properties of microelectrodes, i.e. to assess the recording capabilities of the electrode for neural recording experiments. In a typical two electrode cell system, the microelectrode is immersed in physiological saline solution (0.9 % NaCl) and a small sinusoidal perturbation voltage (5-50 mV) is applied between the microelectrode and the counter electrode (typically a noble metal, e.g. Pt) having a much larger surface area. A small perturbation voltage is needed to ensure that a linear current-voltage response is obtained at each frequency. Measurements are usually taken over a wide frequency region (e.g. 0.1 Hz – 100 kHz) at room temperature. The induced current and its phase are recorded. Typical impedance spectra, measured with a Solartron 1260 impedance gain/phase analyzer (Solartron Analytical, Farnborough, UK) for Pt and Au microelectrodes with diameter of 200 µm is presented in Fig. 5.

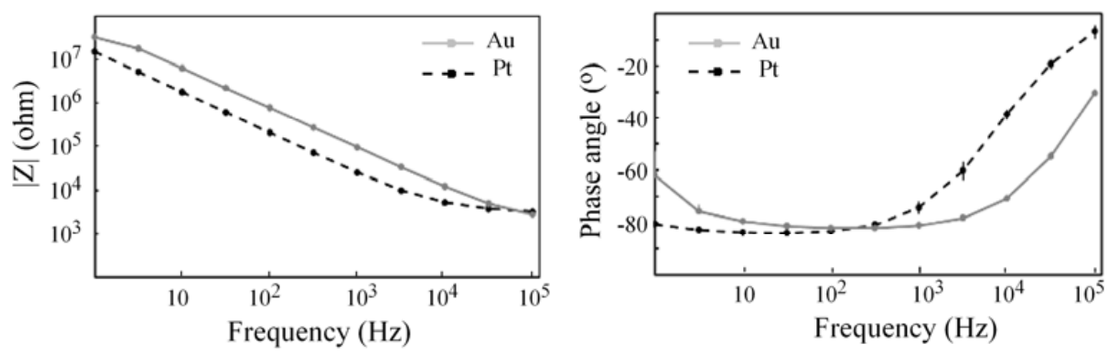


Fig. 5. Impedance magnitude and phase for Pt and Au microelectrodes with a diameter of 200 µm

The EIS results demonstrated that our microelectrodes possessed suitable electrochemical properties for neural recordings. Pt has a much lower impedance level compared to Au especially at low frequencies (below 1 kHz) which are the most relevant in any recordings of cortical signals.

4.2.3 *In vivo* testing

The performance of our microelectrode arrays was tested in acute and chronic recordings in Wistar rats. All animal tests were conducted in accordance with the Council of Europe guidelines and approved by the Institutional Animal Care and Use committee and the State Provincial Office of Eastern Finland.

During the recording sessions, the signals from the electrodes was passed through a preamplifier (Neuralynx Inc., Bozeman, MT, USA) and led into the main amplifier (Grass Instruments, West Warwick, RI, USA) with the data acquisition PC running DataWave SciWorks. Both electrical current and auditory stimuli were used. The square wave current stimuli were of 1 ms duration, and the stimuli of auditory were 10 ms in duration, generated by a WPI (Aston, Stevenage, Herts, UK) isolated current source and led into a piezo buzzer on the front paw of the rat. A stimulus set consisted of paired pulses (a gating paradigm) and the trials were averaged in sets of 25.

Wistar rats were anesthetized with 1.2 – 1.5 g/kg urethane for acute recordings and with a mixture of 0.5 mg/kg medetomidine (Domitor) and 75 mg/kg ketamine (Ketalar) intraperitoneally for implantation for chronic recordings. The rats were placed in a stereotaxic apparatus. Holes for the microelectrode array and for reference electrodes were drilled on the same side of the skull. The microelectrode array was inserted on the dura over the parietal cortex. A stainless steel (SS) screw was used as a reference (ground) electrode placed at A 1.0, L 1.0 with respect to bregma, i.e. 2-3 mm in front of bregma. SS screws also acted as an anchor when the array was cemented onto the skull in the chronic recordings. After anesthesia, the rat was aroused by administration of the antagonist atimepazole (Antisedan), after the surgery. The rats were allowed to recover for a minimum of 7 days before the first experiments. In the chronic recordings, the implanted rat was connected to the recording apparatus and it was either allowed to move freely in the recording box or was gently immobilized by holding it securely in a towel.

The arrays demonstrated excellent flexibility and mechanical strength during handling and implantation onto the surface of rat cortex. During the acute recording session, the microelectrode array was capable of yielding stable readings as observed in the form of the standard response parameters, such as latencies, onsets and decays of the main components in the voltage traces. An example of the somatosensory evoked potential (SEP) recording, obtained 4 hours after the onset of anesthesia is presented in Fig. 6.

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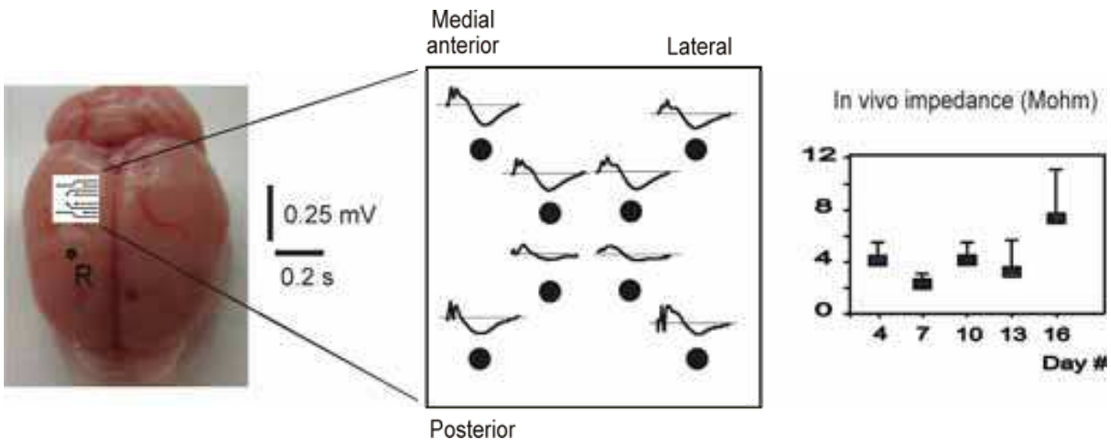


Fig. 6. An example of the *in vivo* somatosensory evoked potential recording in the rat parietal cortex. Profiles of averaged evoked potentials using the 8-channel MEA are shown above the corresponding recording site (black dots). The current stimuli were delivered to the left paw of the rat. The position of MEA and reference screw electrode ("R") is depicted on the brain of a rat after the experiment and its surgical removal. Right graph: average electrode impedance (mean and standard deviation, n = 8) measured *in vivo* with three-day intervals. In chronic recordings, the electrode was capable of yielding signals comparable with the presented acute signals for approximately two weeks after array implantation. Note the impedance jump on day 16, coinciding with a decay in the responses (not shown)

The SEP recordings obtained with our array are comparable in their signal-to-noise ratios with previously published recordings with various electrode materials, such as platinum (Hayton et al., 1999), silver (Kalliomäki et al., 1998) and tungsten (Ureshi et al., 2004). Recordings are also comparable to previous studies with microelectrode arrays (Stett et al., 2003). In chronic recordings, the electrode was capable of capturing a biologically meaningful signal (comparable to signals in the acute experiment) for approximately two weeks after array implantation. However, after 16 days, the responses decayed due to a variety of mechanical and technical reasons. The signal amplitude decreased at the same time as the electrode impedance doubled (Fig. 6). Although no macroscopic scar formation was seen in the examination of the brain after the array was removed, this kind of increase in *in vivo* impedance is compatible with a thickening of the dura, a common finding in chronic experiments, and microscopic growth of non-conductive fibrous tissue around the electrode, shrinking the freely exposed surface area of the recording site.
Our current research is concentrating on improving biocompatibility issues, the array construction and implantation techniques in order to prolong the functional lifetime. The goals of the work include development of nanostructured electrode surfaces by utilizing ultra short pulsed laser deposition (USPLD) techniques or electrolytic deposition methods to improve the electrochemical functionality of electrodes as well as to incorporate functional coatings and/or biological compounds to polyimide layer to reduce the growth of scar tissue in the vicinity of array.

5. Biocompatibility testing

Despite the very challenging microfabrication processes used in electrode fabrication, electrode failures due technical reasons (short-circuits, broken signal transmission lines etc.) are rare, and the stable, long-term functioning of neural implants is mainly determined by the tissue response to chronically implanted electrodes. A general immune activation of the brain in response to the presence of a foreign body implant has been commonly believed to be the main reason for signal deterioration of chronically implanted electrodes (Nicolelis et al., 2003; Edell et al., 1992; Schmidt et al., 1993). Biocompatibility aspects of neural implant materials will therefore be very crucial in the development of new generation chronic implants. In this section, we summarize some *in vivo* implantation and *in vitro* cell culture studies, concentrating particularly on these potential flexible thin film electrode materials that were already discussed in this chapter, i.e. Pt, Au, Ir, polyimide, SU-8, PDMS etc.

5.1 *In vivo* implantation studies

The tissue response to neural implant materials has been widely reported in the literature. Stensaas and Stensaas implanted 27 different materials, consisting of metals and insulators, into the cortices of rabbits. After 30 days, the histological examination revealed no adverse reaction in response to gold, platinum and tungsten (Stensaas & Stensaas, 1978). Moreover, subdural implantations of two common insulators, parylene-C and polyimide (PI-2555), into the cerebral cortex of the cat evoked only minimal tissue reactions after a 16 week implantation period. All neurons situated beneath the implant site appeared to be normal. Tissue reactions to polyimide and parylene-C were comparable to pure platinum (negative control) whereas Ag-AgCl (positive control) had triggered chronic inflammatory reactions (Yuen et al., 1987). In another study, polyesterimide-coated gold wires implanted subdurally on rabbit cortex showed no evidence of toxicity. There was only slight gliosis, and there were no inflammatory reactions present at 16 weeks after implantation (Yuen & Agnew, 1995). On the other hand, polyimide-platinum electrodes implanted to the rat scientic nerve for 3 months were demonstrated to induce a mild scar response and local inflammation reactions, though these were limited to a small area around the electrode (Lago et al., 2007).
Unfortunately all artificial materials implanted in the CNS have an inconvenient tendency to induce significant glial scar tissue formation (Polikov et al., 2005). This gliotic scar tissue is attributable mainly to glial cells such as astrocytes and microglia and it poses one of the greatest challenges in the field of neural prosthetics. The formation of scar tissue can cause serious impairment of implant performance due to decreased local density of neurons and the formation of an encapsulation layer that increases electrode impedance and lowers the signal amplitudes. Astrocytes that account for 30-65 % of glial cell population in the CNS are able to secrete 8-10 nm diameter intermediate filaments of polymerized glial fibrillary acid protein (GFAP). When the electrode is implanted into the CNS, the astrocytes become activated and they transform into reactive phenotype which produces much larger size GFAP filaments and there is also enhanced cell proliferation and migration capacity. GFAP is the most commonly used astrocyte specific cell marker with which to assess the level of scar formation after electrode implantation. The brain slices of rats used in the chronic experiments are in cultured with anti-GFAP staining antibodies. GFAP- positive cells are counted around the implantation area of the cortex in order to estimate the extent of astrocyte activation and gliosis. In previous studies with probe-type electrodes, it has been

shown that the astrocyte response to brain injury can be divided into two phases, the early response that occurs immediately after electrode implantation and the long-term chronic response. It has been reported that the number of astrocytes and microglia is significantly increased in the area surrounding the silicon probes (Szarowski et al., 2003; Turner et al., 1999) within a few hours after insertion. The extent of this early response is dependent on probe size, shape and surface roughness (Szarowski et al., 2003). The long-term response, starting approximately one week after electrode implantation (Norton et al., 1992), consists of a compact glial scar tissue formation surrounding the electrode and which ultimately isolates the microelectrodes from neurons/neural tissue elevating the impedance and causing signal deterioration (Nicolelis et al., 2003; Edell et al., 1992; Schmidt et al., 1993).

5.2 *In vitro* cytotoxicity

In vitro cytotoxicity tests play an important role in evaluating the biocompatibility properties of potential novel materials. The international standard "Biological evaluation of medical devices: tests for *in vitro* cytotoxicity" (ISO 10993-5) describes the test methods to assess the *in vitro* cytotoxicity of implant materials and medical devices. The mammalian cell line is selected according to the intended application. Cells are seeded in contact with a tested material and/or with an extract of a test material and different parameters are evaluated such as cell adherence, adhesion, proliferation, morphological changes and metabolism changes.

Kotzar et al. (2002) performed an *in vitro* cytotoxicity evaluation of a wide variety of materials used in microelectro-mechanical systems (MEMS) including Si, thermal oxide, n-doped polysilicon, Si_3N_4, Ti, SU-8 and silicon carbide. Minimal cytotoxicity was demonstrated for these materials.

Polyimides have been shown to be non-cytotoxic in many *in vitro* studies (Richardson et al., 1993; Stieglitz et al., 2000). Stieglitz et al. (2000) studied the cytotoxicity of three commercial polyimide grades (Pyralin PI 2611, PI 2556, PI 2566, HD Microsystems) and reported excellent biocompatibility for PI 2611 and PI 2556 and good results for PI 2566. This last polyimide, since it is fluorinated, differs from the others with respect to its chemical structure. Furthermore, Lee et al. (2004b) reported that fibroblast cells attached, spread out and grew on polyimide surfaces in a corresponding manner to the behaviour of control cells growing on the surface of polystyrene. However the previously tested polyimides are mainly non-photosensitive. In a recent study, Sun et al. (2008) assessed the biocompatibility of a photosensitive polyimide for use in an implantable medical device. They concluded that the photosensitive polyimide (Fujifilm Durimide 7020) was also noncytotoxic and the fibroblast (L929) cell adhesion, morphology, and spreading was even enhanced on the photosensitive grade than one non-photosensitive grade (HD Microsystem PI-2611).

Figure 7 presents fibroblast cells (BHK-21) cultured on polyimide (Pyralin PI-2525, HD Microsystems GmbH), high-density polyethylene (negative control) and latex rubber (positive control) after 24 h incubation period. Only a few cells are seen on cytotoxic latex rubber whereas the cell density on polyimide is even higher than on PE demonstrating the excellent biocompatibility of this polyimide grade.

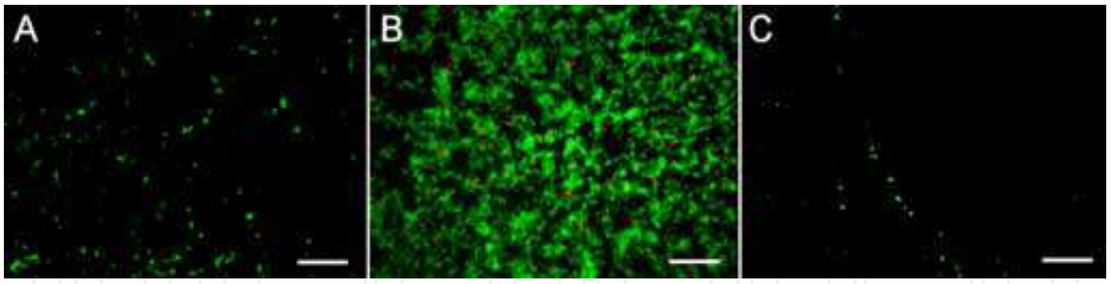


Fig. 7. Live/dead staining of BHK-21 fibroblast cells cultured on the surfaces of (A) polyethylene (negative control), (B) polyimide (C) latex rubber (positive control) after a 24 hour incubation period. Confocal laser microscope image, viable cells: green, dead cells: red, scale bar = 200 μm

The optimal electrode site should support neuronal cell attachment and growth. Thanawala et al. (2007) studied the biocompatibility of metal thin films *in vitro* cell culture studies. The results showed that iridium oxide and platinum thin films are biocompatible and non-toxic for neural cell (cortical rat neurons) growth. Furthermore, Pt films were reported to be superior to iridium oxide films in their ability to support cell attachment.

6. Future trends and strategies to improve the long-term performance of implanted electrodes

Surface modifications of materials intended for implantation are needed in order to improve the functionality and biocompatibility of implanted electrodes, i.e. to reduce the formation of the glial scar, prevent inflammatory reactions and extend the functional lifetime of the implanted devices, and this is an area in which there is intensive worldwide research. It must be noted that there are different requirements for different parts of a neural implant. Recording electrode sites should remain bare to achieve good signal output whereas encapsulation materials should be allowed to be covered by tissue cells like fibroblasts in order to allow them to co-exist in the human body. In this section, we will concentrate on future trends and strategies to improve the long-term performance of neural implants by dividing them into two categories: material science and bioactive molecule strategies.

6.1 Material science strategies

It is well-known that the there is an inverse relationship between electrode impedance and its surface area. Therefore, it is advantageous to develop microelectrodes with high nanoscale surface topography since in this way it will be possible to achieved high effective surface area without increasing the geometrical surface area. Electrodeposition of platinum (Pt black) is a classic technique which can increase surface roughness and lower electrode impedance (de Haro et al., 2002). Other common surface modification techniques used to increase nanoscale roughness are wet etching of gold and activating of iridium to form a nanoporous iridium oxide layer. Different etching and machining techniques (e.g. reactive ion etching, laser ablation etc.) can be also used to form different micro/nanostructures, e.g. grooves and wells onto the surface of the substrate upon which the electrode material can then be deposited using traditional thin film techniques. On the other hand, USPLD (Phipps, 2007; Eason, 2007) can be used both to deposit thin films and to create a nanostructured

surface in a well-controlled and straightforward manner without the need for several process steps. An example of nanostructured Pt surface from our experiments is shown in Fig. 8. The size of the features is about 30 nm in this case. Furthermore, it is possible to combine micro/nanomachining using ultra short pulsed laser ablation and deposition to create well controlled and high quality surface textures like grooves, wells, holes etc.

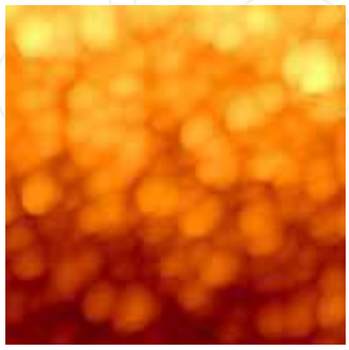


Fig. 8. AFM image of nanostructured Pt surface deposited using the USPLD technique. The average size of Pt particles is 30 nm

It has been also shown that electrode surface morphology has a strong influence on neurocompatibility. Enhanced functions of neurons have been demonstrated on biomaterials structured at the nanoscale (Bayliss et al., 1999; Raffa et al., 2007). Raffa et al. (2007) used focused ion beam technology as a nanometric precision machining technique to modify the surface morphology of tungsten, and studied the effect of the nanofeatures on adherence and adhesion of PC12 neural cells. They concluded that the ability of PC12 cells to adhere to the surface is strongly linked to the dimensions of nanofeatures and the feature size of 25 nm is superior than 270 nm material. Positive interactions between neurons and nanostructured silicon surfaces with 10 nm pores have been also shown (Bayliss et al., 1999). However, there is one report of decreased astrocyte adhesion and increased extension of neuritis on nanoporous silicon surfaces (Moxon et al., 2004). Decreased adhesion, reduced proliferation and less long-term functional activation of astrocytes on carbon nanofiber materials (fiber diameter 60 nm) compared to conventional carbon fibres (diameters in range of 125-200 nm) have also been demonstrated (McKenzie et al., 2004). These results provide evidence that nanoscale materials may have a promising future, i.e. they increase effective surface area of electrode and interact positively with neurons but at the same time they reduce the functions of astrocytes leading to decreased glial scar tissue formation.

As discussed before, conventional lithographic techniques can be combined with thin film techniques like evaporation, sputtering or electrodeposition. In spite of their widespread use, for example in the electronics industry, they have some shortcomings in electrode preparation compared to some novel techniques such as USPLD. In this study, we utilized Coldab™ USPLD configurations developed by Picodeon Ltd, Finland. This technique (Amberla et al., 2006) has several advantages in thin film preparation such as high adhesion, smooth or nanostructured surface topography and the possibility to deposit films or particles on heat sensitive substrates. Furthermore, different kinds of materials (polymers, metals or ceramics) can be used as a source to prepare single material films or composites, i.e. multilayer structures or homogeneous or graded composite films. High purity source

materials available in a solid form can be utilized and transferred from the target to the sample in a stoichiometric manner. Due to the significant increase in power produced by picosecond pulsed lasers during recent years, this deposition technique has acquired commercial state, i.e. it can be used for deposition on large surfaces (in dimensions of ten centimetres), not just on small laboratory test samples. Thus USPLD technique holds an evident potential for neural electrode development.

The USPLD is a very effective method to convert a material so it can be deposited as a plasma, atom or molecular beam to produce bioinert, biocompatible, bioactive or bioresorbable films without generating extra heat on the sample surface (Eason, 2007). Therefore, the sample remains normally very close to room temperature and it is possible to deposit thin films on heat sensitive materials like polymers, which can be utilized in flexible electrodes or as a photoresist. Samples containing polymeric materials can be kept at low temperatures during the deposition and thus avoid hardening or flow during deposition. This leads to smooth high quality films and easy lift-off in the case of lithography. Since the target materials remain almost at room temperature, no water cooling is needed which is convenient since different target materials and dimensions can be utilized. Expensive target materials like Pt, Au, Ir or ITO can be used effectively and they remain free from contamination. Since one has many possible material choices, the material combinations can be optimized with respect to signal stability, biocompatibility, cell attachment, antibacterial properties etc. Enhanced surface properties can be achieved by including appropriate surface modifying layers: these can be organic compounds like collagen, fibronectin or even cells.

If USPLD is used in the creation of deposition electrodes, one important advantage compared to several other methods, is that the growing film does not contain microparticles or droplets, which would cause pinholes in the films. This is due to the fact that the laser ablation pulse is so short that the energy penetrates to only very shallow (tens of nanometers) surface layer which is effectively converted to plasma and the target surface remains smooth without any flows or deteriorations. The quality of the film becomes an important issue, for example in the case of insulator films for neural sensors. Based on our tests, these films do not seem to contain any microdefects which could lead to short circuiting especially in liquids. In addition to ceramic insulators like alumina (Al_2O_3), polymers can be deposited with the same technique. The ultrasmoothness of deposited coatings might provide an additional benefit to avoid scar tissue formation, inflammation reactions or activation of glial cells.

6.2 Strategies involving anti-inflammatory agents and bioactive molecules

Several strategies are currently being studied to discover effective methods to minimize the immune response and inflammation around the neural implant as well as to encourage neural growth at electrode sites (Polikov et al., 2005; Zhong & Bellamkonda, 2008). Anti-inflammatory agents, such as dexamethasone (DEX) can be used to minimize the release of inflammatory mediators and to attenuate the formation of a fibrous capsule. DEX and other pharmaceutical agents can be administered in several way e.g. subcutaneous injection (Shain et al., 2003; Spataro et al., 2005) and the local release from electrode coatings of the drugs as incorporated agents (Zhong & Bellamkonda, 2007; Kim & Martin 2006). It is believed that the local delivery of DEX reduces the inflammatory tissue response and prevents the elevation in electrode impedance more effectively compared to peripheral

injection since in the latter case there may be difficulties in the drugs crossing the blood-brain barrier and chronic use of corticosteroids can evoke several side effects, such as myopathy and diabetes (Zhong & Bellamkonda, 2007). Additionally, Si-based microelectrode arrays have been developed with integrated microfluidic drug delivery channels through which the bioactive molecule was released (Retterer et al., 2004; Rathnasingham et al., 2004). In addition, flexible multi-channel polyimide recording probes with incorporated small pores and wells that can be selectively filled with a dextran hydrogel and bioactive species such as nerve growth factor (NGF) (Rousche et al., 2001) as well as devices containing microfluidic channels for drug delivery (Metz et al., 2004) have been developed.

Several bioactive molecules are being investigated as potential binding molecules to promote the adherence and functions of neurons at the electrode site. Instead of using intact cell adhesion proteins such as collagen and fibronectin (Ignatius et al., 1998), new research efforts are concentrated on functionalizing the electrode surfaces with relevant protein sequences such as RGD, YIGSR and IKVAV (Polikov et al., 2005; Kam et al., 2002). It has been demonstrated that functionalized surfaces with these kinds of protein sequences can be used to support neuronal growth or repel glial growth. Furthermore, peptides can be deposited in patterns by using soft lithographic (Xia & Whitesides, 1998) techniques intended to guide cellular outgrowth.

7. Conclusion

Modern microfabrication techniques offer great opportunities in the development of novel implantable neural interfaces for recording and stimulating purposes. Miniaturized electrode arrays with high-channel densities are now in common use in animal models, but their human counterparts are still mainly being investigated or at best undergoing clinical trials. Silicon has been the mostly utilized substrate material despite its rigidity, but recently there has been a growing interest toward polymeric implant materials that could be flexible enough to mimic biological tissue and to reduce adverse tissue reactions. Despite the very challenging microfabrication processes used in electrode fabrication, electrode failures due technical reasons are rare, and the stable, long-term functioning of neural implants is mainly determined by the tissue response to chronically implanted electrodes. Therefore, current investigations are now concentrating on the evaluation of the tissue-electrode interface aiming to improve the functionality and biocompatibility of implanted electrodes, i.e. to reduce the formation of the glial scar, prevent inflammatory reactions and extend the functional lifetime of the implanted microdevices. Further development of implantable neural electrodes promises to deliver novel options to acquire more detailed information of brain functions, to plan more precise surgical operations as well as improving the quality of life for many patients suffering pain or from loss of neural functions.

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The field of biomedical engineering has expanded markedly in the past ten years. This growth is supported by advances in biological science, which have created new opportunities for development of tools for diagnosis and therapy for human disease. The discipline focuses both on development of new biomaterials, analytical methodologies and on the application of concepts drawn from engineering, computing, mathematics, chemical and physical sciences to advance biomedical knowledge while improving the effectiveness and delivery of clinical medicine. Biomedical engineering now encompasses a range of fields of specialization including bioinstrumentation, bioimaging, biomechanics, biomaterials, and biomolecular engineering. Biomedical engineering covers recent advances in the growing field of biomedical technology, instrumentation, and administration. Contributions focus on theoretical and practical problems associated with the development of medical technology; the introduction of new engineering methods into public health; hospitals and patient care; the improvement of diagnosis and therapy; and biomedical information storage and retrieval. The book is directed at engineering students in their final year of undergraduate studies or in their graduate studies. Most undergraduate students majoring in biomedical engineering are faced with a decision, early in their program of study, regarding the field in which they would like to specialize. Each chosen specialty has a specific set of course requirements and is supplemented by wise selection of elective and supporting coursework. Also, many young students of biomedical engineering use independent research projects as a source of inspiration and preparation but have difficulty identifying research areas that are right for them. Therefore, a second goal of this book is to link knowledge of basic science and engineering to fields of specialization and current research. The editor would like to thank the authors, who have committed so much effort to the publication of this work.

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