

Integration of Microfluidic Capabilities into Micromachined Neural Implants

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ABSTRACT

Several approaches for micromachined neural implants have been established worldwide to deliver neuroscientific tools to investigate the function of the brain. Bioelectrical signals of single cells as well as of synaptic background activity have been recorded via multichannel electrode systems and the effect of electrical stimulation has been used to treat diseases or to partially restore sensory functions. However, the brain does not work only electrically but chemical and electrical signals strongly interact. Therefore, chemical analysis of the metabolism of the brain and neurotransmitters is of high interest as well as delivery of chemical substances to modify signal transduction and generation in the brain. This article presents existing micromachining approaches of electrical neural probes for intracortical recording and microfluidic channels, pumps and valves to realize drug delivery and probe sampling. Application scenarios will be discussed with respect to the opportunities and limitations of the technical systems.

Keywords: bio-MEMS, neural implant, recording, stimulation, micro fluidic, drug delivery, micropump, micromachining

1. INTRODUCTION

The brain as central control of the body fascinates physicians, natural scientists and engineers since centuries. The knowledge about anatomical structure, fundamental chemical and electrical processes and the interaction of single cells as well as complex subcortical structures and cortical areas has grown tremendously in the last decades. However, the brain with billions of nerve cells and trillions of synaptic connections between nerve cells is not fully understood today. Trauma and neural degeneration cause diseases and disabilities in millions of persons. The numbers will especially increase in Western industrial countries in the next decades and other countries later on, if aging societies promote neurodegenerative diseases. Restorative neurology addresses diagnosis, therapy and rehabilitation of trauma of the peripheral and central nervous system, stroke and neurodegenerative diseases like Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease, macula degeneration, retinitis pigmentosa, and multiple sclerosis. Many scientists work on translational research to bring potential therapeutic strategies into clinical practice. Research lines include stem cell therapy, immunotherapy, gene therapy, pharmacotherapy, neuroprostheses, functional electrical stimulation, and "deep brain stimulation". Physicians, biologists, chemists and engineers have to work closer, since interdisciplinary research is mandatory to meet the requirements of nowadays challenges. In this context, neural engineering entered the scene about one decade ago as a relatively new discipline that applies engineering methods to investigate neural processes on all levels of the nervous system. The development of tools is one

challenging part of this science that might help to understand how the brain works. Or at least to invent a device that helps to make better diagnoses and to improve the activities of daily living of persons that have disabilities or suffer from neurological diseases.

One of the work horses in neuroscientific investigations is the microelectrode, either drawn from a metal wire or from a glass pipette to record bioelectrical signals and to electrically stimulate nerve cells. In diagnosis, the use of electrical signals is widespread in the peripheral and central nervous system [1]. The interaction with the nervous system, often summarized in the terms of neural prostheses and neuromodulation, has transferred only few devices into clinical practice [2]: cochlear implants restore hearing, spinal cord stimulation alleviates chronic pain and urge incontinence, and deep brain stimulation diminishes the symptoms of Parkinson's disease and has been recently approved as method to treat severe obsessive-compulsive disorder. Vagal nerve stimulation as therapy in medical refractory epilepsy and in severe psychiatric disorders has been also successfully approved in the last decade. There is a trend to use miniaturized systems [3] as neural implants where robust and reliable precision mechanics solutions do not match the requirements of size and large scale integration, e.g. in the development of vision prostheses and brain-computer interfaces. Several start-up companies are currently in clinical trials to prove the safety and efficacy of retinal vision prostheses [3][4] to enter the market soon. Brain-machine interfaces are still in a developmental state [5][6][7] even though a first device has been implanted for 18 month into a spinal cord injured person [8].

For fundamental investigations in neuroscience, however, several approaches of micromachined neural probes (Fig. 1) and implants have been established worldwide to investigate the function of the brain.

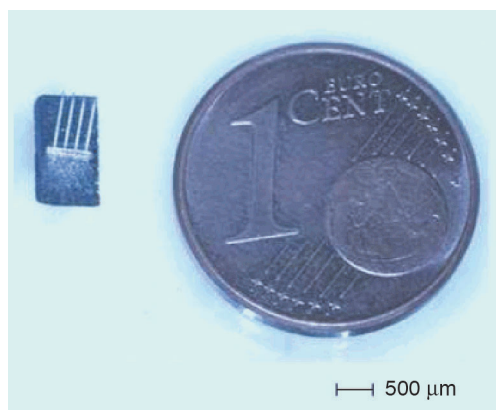


Figure 1. Example of a silicon based neural probe (placed on a silicon die).

Bioelectrical signals of single cells as well as of synaptic background activity have been recorded via multichannel electrode systems and the effect of electrical stimulation has been used to treat diseases or to partially restore sensory functions. However, the brain does not work only electrically but chemical and electrical signals strongly interact. Pharmaceutical intervention is still the gold standard in all neurological diseases. Chemical analysis of the metabolism of the brain and neurotransmitters is of high interest as well as delivery of chemical substances to modify signal transduction and generation in the brain. This review tries to summarize existing micromachining technologies and approaches to integrate components into systems that are able to combine electrical and chemical interaction with the nervous system. Basic manufacturing techniques of neural probes, microfluidic channels and pumps are introduced and will be discussed with respect to their opportunities and limitations within a multimodal implant for fundamental neuroscientific investigations and clinical applications in diagnosis, therapy and rehabilitation.

1.1 Neurotransmitter release in neuronal diseases

The release of neurotransmitters is disturbed in neuronal diseases. If one could release these transmitters by technical means, e.g. by triggering the drug releasing cells or by technical drug delivery via implanted systems, new therapies to treat these diseases could be invented. A very brief introduction into this topic gives basic information and helps to understand the rationale behind all research to develop multifunctional microimplants to interact with the brain by electrical and chemical means.

Major neurological disorders are related to neurotransmitter release (all data taken from [9]).

Motor disorders like

- Alzheimer's (Acetylcholine, glutamate, norephedrine, serotonin),
- Dystonia (dopamine),
- Epilepsy (γ -aminobutyric acid: GABA),
- Essential tremor (GABA, dopamine), and
- Parkinson's disease (dopamine)

are effected as well as neuropsychological disorders like

- Anorexia/bulimia (serotonin, norephedrine, dopamine),
- Anxiety (norephedrine),
- Depression (dopamine, serotonin, noradrenaline),
- Mania (serotonin),
- Obsessive-compulsive disorder (serotonin),
- Schizophrenia (dopamine, noradrenaline, acetylcholine, glutamate, GABA),
- Tourette's syndrome (dopamine, glutamate, GABA, serotonin).

Studies in animals have shown that electrical stimulation of cells in dedicated areas in the brain is able to release these neurotransmitters, if the right stimulation parameters (amplitude, repetition frequency, duration) are chosen [9]. This knowledge has been transferred into therapies of deep brain stimulation, vagal nerve stimulation (see also [2]) and transcranial magnetic stimulation in many diseases. Reference [9] gives a broad overview and leads to further more detailed references.

Even though therapies have been successfully transferred into clinical practice, the understanding of the underlying principles is still poor. More sophisticated (implantable) tools with good temporal and spatial selectivity can help to gather more knowledge and develop better therapies with fewer side effects.

1.2 Multimodal neural probes

In neuroscientific investigations but also in medical applications, not only the electrical signals but also the "environment" around the implanted probe is of interest. To understand both, the function or malfunction of the area under observation or treatment and the tissue material interface, sensors and actuators for several modalities have to be considered (Fig. 2). Nerve cell activity is electrical by origin and can be recorded by electrodes as well as electrical stimulation is suitable to excite these cells. The cell activity and signal transmission and processing in the neuronal networks, however, is strongly dependent of the concentration and the balance of several neurotransmitters in the background (see paragraph above). The monitoring of the neurotransmitters and the neurotransmitter releasing cells as the interaction with them is of high interest for therapy of diseases [10][11][12]. The composition of the extracellular fluid [13] is analyzed and choline, glutamate [14] and γ -aminobutyric acid (GABA) [15] are transmitters to be monitored. Depending on the disease or research interest, dopamine and serotonin are also of high interest. Integration of chemical sensors and focal drug delivery within neural probes could cover this objective. Chemical but also optical sensors are mandatory to determine the cell metabolism. Especially by (optically) monitoring absorption spectrum of haemoglobin, detailed information about blood perfusion and oxygen supply of the brain can be gathered [16][17]. Optical spectroscopy, also for the application of optical coherence tomography as method to image the tissue layers around the probe and optical stimulation of normal or genetically modified tissue are exciting new opportunities but go beyond the scope of this review.

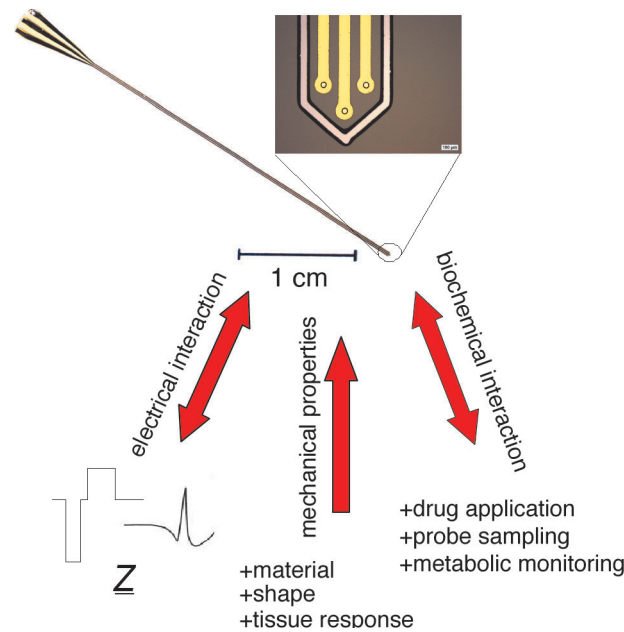


Figure 2. Requirements of a multifunctional, multimodal neural probe. Example: polyimide based probe.

Even though thousands of persons benefit from electrically active (neural) implants like cardiac pacemakers and cochlea implants, any implant is still a foreign body that is attacked after implantation. In the best case the implant is bioinert, i.e. it leads to a defined tissue reaction that results in a fibrotic tissue capsule. The material-tissue surface interaction—also called surface biocompatibility—often starts with unspecific protein absorption—so called biofouling—that triggers the foreign body response of to attack the implant. Therefore, substrates or coatings must be chosen to act as a reasonable good biomaterial [18]. In addition the mechanical interaction between the implant and the surrounding tissue—called structural biocompatibility—lead to cellular reactions that attack and encapsulate the implant [18]. Electrical stimulation might also stress and harm the surrounding tissue if certain limits of charge are exceeded. Corrosion products of the electrodes, pH shifts during stimulation and the decomposition of water and proteins have to be prevented [19]. The biocompatibility of the implant materials is one of the fundamental challenges in implant development but goes also far beyond the scope of this review. Here, some monitoring opportunities to detect these reactions shall be reviewed. The protein adsorption on surfaces can be monitored [21] but needs separate electrodes as transducers that cannot be used for other purpose. The encapsulation of implants [22], however, can be monitored with existing recording or stimulation electrodes. Its use has been already transferred into clinical applications of cochlea implants [23]. Monitoring of the tissue response to neural probe implantation has been recently introduced and allows to predict the encapsulation of the implant with a continuous non destructive measurement method in vivo [24][25].

The integration of all these measurement modalities into a single neural probe is challenging, especially if the systems shall be stable over decades in human use. The feasibility to use neural probes with integrated drug delivery has already been shown in animal studies [26] and is motivating to design and develop concepts and devices for multimodal intracortical neural implants.

2. CONCEPTS, MATERIALS AND MANUFACTURING TECHNOLOGIES

Design and development of multifunctional and multimodal neural implants requires a broad knowledge of materials, process technology, assembling, and packaging. Existing concepts of devices and systems from other applications should be known to prevent the “reinvention of the wheel”.

In the ideal design, all aspects of monitoring of electrical and (bio-) chemical activity of the brain should be combined with actuation capabilities to interact electrically or chemically with small ensembles of nerve cells in a closed-loop control (Fig. 3). Electrodes for recording and stimulation, electronic circuitry for multiplexing a large number of channels, amplification, and stimulation are integrated as well as biochemical sensors, pumps and valves for drug delivery and sampling. Integrated sensors monitor the flow rates and the level of drugs in the reservoir. The assembled and packaged system is equipped with energy supply and data transmission capabilities to send diagnosis data and alerts, e.g. to remind the patient to visit his or her physician for a refill of the drug reservoir. The materials used do not provoke tissue reactions but get integrated in the cellular environment. This vision is still fiction but should be in the designers mind to address all aspects, even he or she is only working on a single piece of the puzzle.

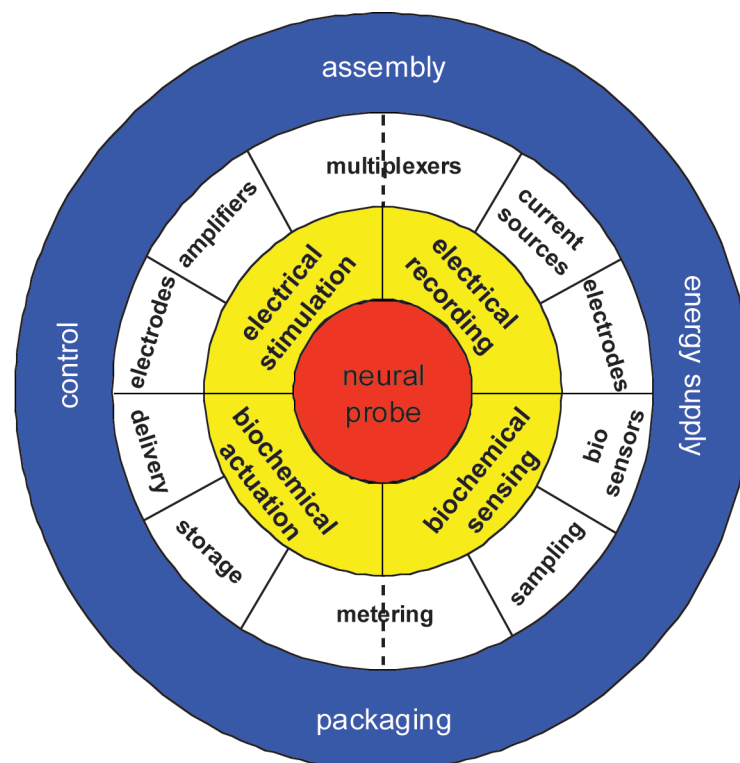


Figure 3. Functions, components and technologies of a multifunctional, multimodal neural probe.

Neural probes just need electrodes, interconnection cables and contact pads to record bioelectrical signals and to stimulate neurons. The different process technologies to manufacture these probes will be reviewed in the next paragraph. If drug delivery and probe sampling is included, the systems get more sophisticated (Fig. 4).

Drugs have to be transported from a reservoir to the target tissue or fluidic samples have to be taken and to be analyzed at the spot or at a sensor somewhere else in the system. For these tasks, microchannels have to be integrated in the probes and micropumps have to transport the fluids through the channels. If these systems shall work on demand according to patient specific needs, flow sensors and signal processing have to be integrated into the system to obtain closed-loop control. Anatomical space limitations have to be taken into account as well as temperature limits (a maximum of 1 K body temperature increase is allowed by regulations). Local drug delivery of small volumes and cell ensembles also requires low dead volumes in the delivery or sampling system. The proteins and cells

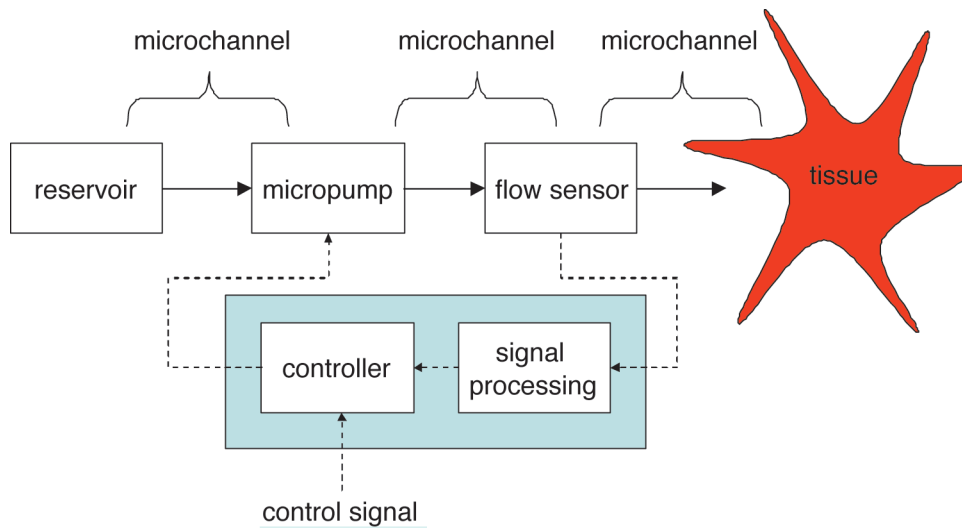


Figure 4. Schematic view of a drug delivery system.

around the implanted probe tend to adhere on the surface and to block small openings. Mechanisms to close these openings, e.g. by passive shutters [27], are one opportunity to solve this challenge. In addition, fluidic cables and reservoirs are components that are still limiting the degree of miniaturization in micromachined neural implants.

The following paragraphs introduce the most common technologies to manufacture the core components of neural implants with microfluidic capabilities for intracortical applications: the probes itself, microfluidic channels and micropumps for delivery and sampling of fluids.

2.1 Manufacturing of intracortical probes

The idea of micromachining of intracortical neural probes goes back to the late 1960ies [28]. Since then, silicon as well as polymer micromachining developed tremendously. Many research groups entered the field for a shorter or longer research period. Nowadays, two standard types of silicon probes have been established: the so-called Utah Electrode Array (University of Utah, Salt Lake City, UT, USA; commercialized by Cyberkinetics, now Blackrock) [36] and the Michigan probe (University of Michigan, Ann Arbor, MI, USA; commercialized by Neuronexus) [30]. In addition, variations of the Michigan process have been launched in Europe within the “Neuroprobes” consortium [31], and flexible polymer-based probes have been introduced by some groups [33][34][35]. This review describes only the most common types of intracortical neural probes. A more detailed description about neural interfaces with the central nervous system can be found in [5]. The different processes to manufacture these intracortical electrode arrays will be shortly introduced. The very details of the different technologies are all reported in the given references.

The Utah Electrode Array (UEA) is the only system in which the electrodes are manufactured out of plane, i.e. out of a “block” of silicon [36] with a thickness between 1.0 mm and 1.5 mm thickness (Fig. 5, a1/2). After p-doping of conductive tracks through the silicon, it is cut in pillars with a dicing saw (Fig. 5, b1/2). These square shaped pillars are wet-etched in different steps (static and under rotation) to form round and sharp needles (Fig. 5, c1/2). Metal is deposited onto the tips of the needles and the shafts are electrically insulated. In most cases, parylene C is taken as insulation and sputtered iridium oxide (SIROF) as electrode material.

The Center for Neural Communication Technology at the University of Michigan has followed an in-plane manufacturing process (Fig. 6) with additional three dimensional electrode assembly [30] after the process [37]. These probes can be either without integrated electronic circuitry, i.e. passive, or active, i.e. with integrated electronic circuitry for signal processing [38]. The process starts with a boron

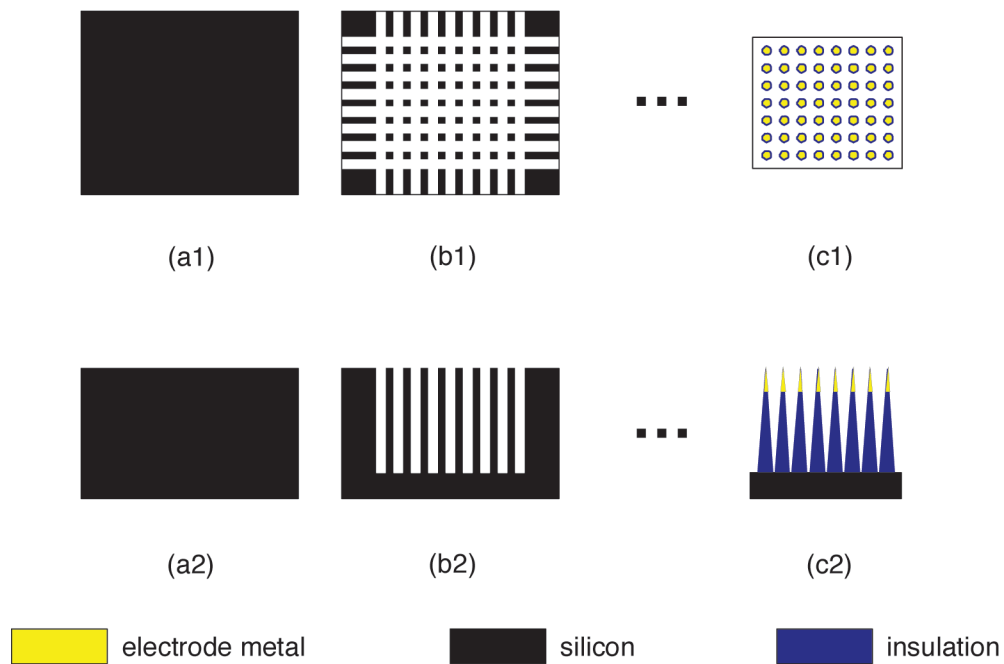


Figure 5. Schematic view of the fabrication of the "Utah Electrode Array (UEA)". Upper row: top view; lower row: side view. Dimensions are not in scale.

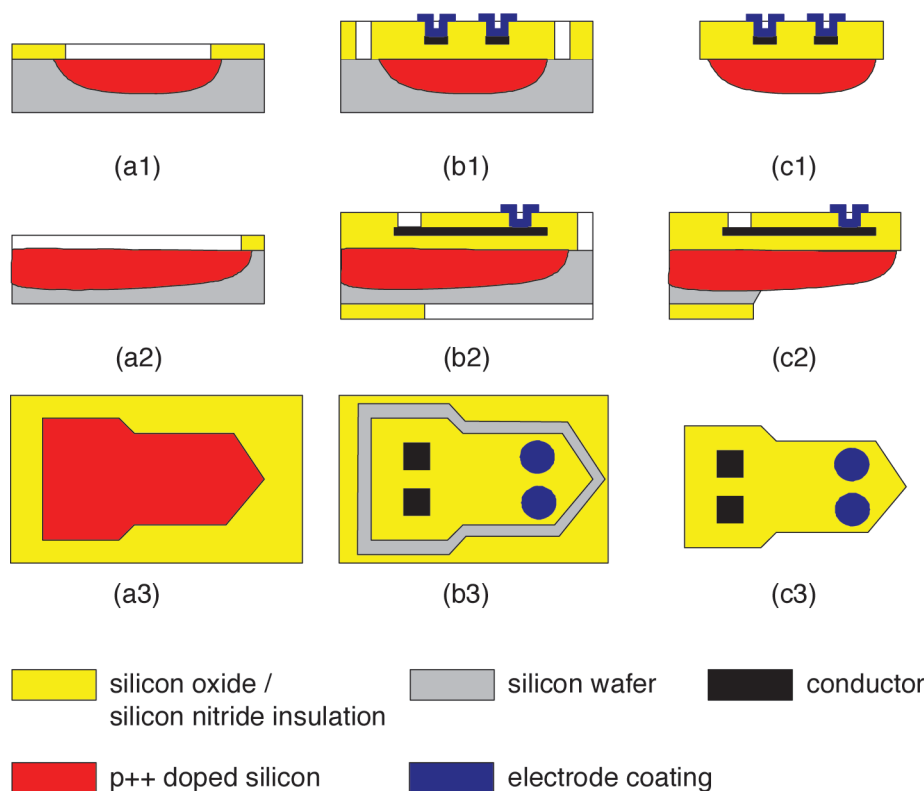


Figure 6. Schematic view of the fabrication of "Michigan/Neuronexus Probes". Upper row: cross section; middle row: longitudinal section; lower row: top view. Dimensions are not in scale.

diffusion to obtain a p-doped area that finally forms the shafts of the probe (Fig. 6, a1/2/3). A stack of silicon nitride and silicon oxide is deposited to insulate a conducting layer that is deposited with means physical vapor deposition (PVD) and structured before a second stack of insulators is deposited. Openings for electrode sites and contact pads are dry-etched with reactive ion etching (RIE). The electrodes are coated with iridium oxide that is structured in a lift-off process (Fig. 6, b1/2/3). The final probes are generated by wet etching with boron etch stop technology: the wafer is etched in ethylene pyrochatechol (EDP) that dissolves anisotropically the silicon (Fig. 6, c1/2/3). Depending on the depth of the boron diffusion, probes can be fabricated with a thickness down to 5 μm at the tip. However, 15 μm to 30 μm became more or less a standard thickness. The silicon dramatically changes its mechanical properties at this thickness and can be bend like any flexible material in the Hookian regime.

The Neuroprobes approach slightly varies from the Michigan process (Fig. 7). The main difference in process technology is the replacement of the boron etch stop process by a deep reactive ion etching to realize thin probe shafts [39]. Silicon dioxide/silicon nitride stacks are not only deposited on the front side to insulate the conductors but also on the back side of the wafer to serve as etch mask for RIE (Fig. 7, a1/2/3). The electrodes are dry etched from the front side to open the electrode sites and connection pads. In a second step, the insulation on the backside of the wafers is structured (Fig. 7, b1/2/3). DRIE is used to thin the electrode shafts and to separate the probes (Fig. 7, c1/2/3). Electrode shafts are about 100 μm and rectangular in cross section. Electrode material is platinum or iridium oxide depending on the electrode diameters that vary from 20 μm to 50 μm in diameter. Flat polyimide cables are attached to the electrodes. They allow implantation in recording chambers that are used in neuroscientific setups. Implantation is feasible without the use of ballistic inserters. Signal to noise ratio of single unit recordings after implantation in the cortex is comparable to the established concepts. However, chronic behavior of the probes still has to be investigated.

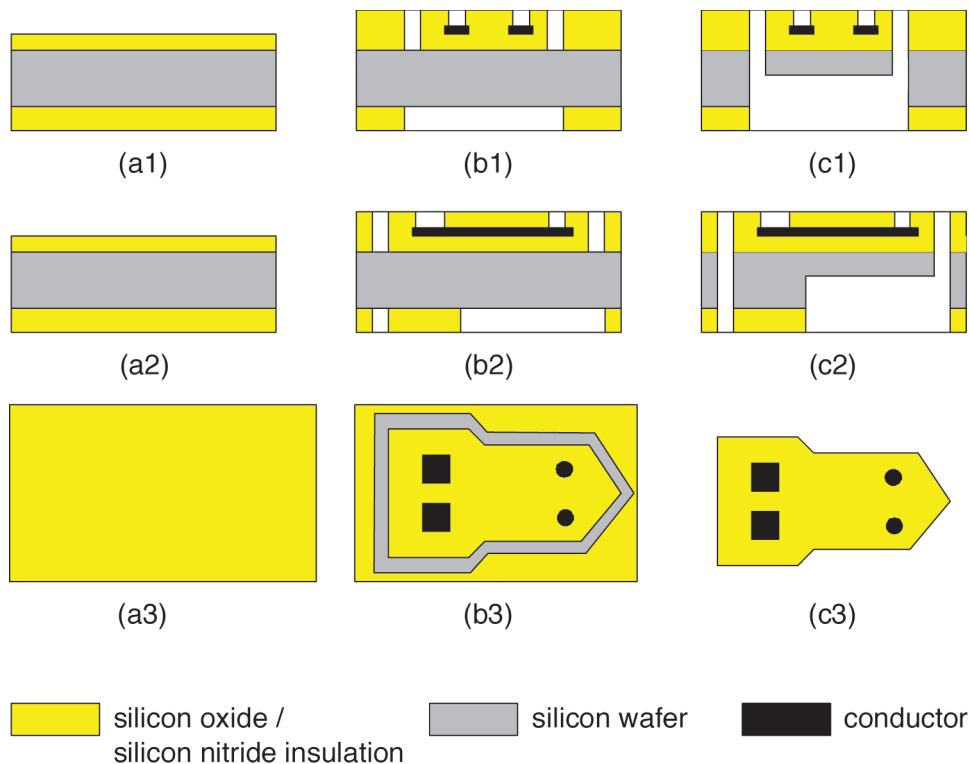


Figure 7. Schematic view of the fabrication of "Neuroprobes". Upper row: cross section; middle row: longitudinal section; lower row: top view. Dimensions are not in scale.

Flexible polymer based neural probes have been developed in addition to the silicon ones in the last 15 years. In most cases, polyimide has been chosen as substrate and insulation material. A polyimide precursor is spin coated on a support wafer and cured at temperatures about 450 °C (Fig. 8 a1/2/3). Metal is deposited and structured to form electrode sites, interconnect tracks and contact pads (Fig. 8 b1/2/3). The electrode sites and contact pads as well as the perimeter of the devices are etched by RIE. In a last step, the devices are separated from the wafer (Fig. 8 c1/2/3) either by mechanical means [40] or by wet etching of a sacrificial layer that has been deposited on the wafer prior to the polyimide process [41]. Recordings have been done with chronically implanted probes with a thickness of 15 µm in rats [41]. Even probes of 10 µm thickness could be inserted in human brain tissue after transfer in a U-shape [42]. However, the insertion of flexible probes still has to be solved if their flexibility further increases. The chronic compatibility of all approaches still has to be improved for all probes, no matter if they are made out of silicon or polymers. Tissue reactions encapsulate the probes and degrade the signal quality [43]. The micromovements between the material and the brain during ventilation and due to blood flow leads to chronic reactions and prevent termination of the foreign body reaction after implantation. Here, significant improvements in science and technology are needed to get a stable neuro-technical interface at the cellular level that works reliably over decades.

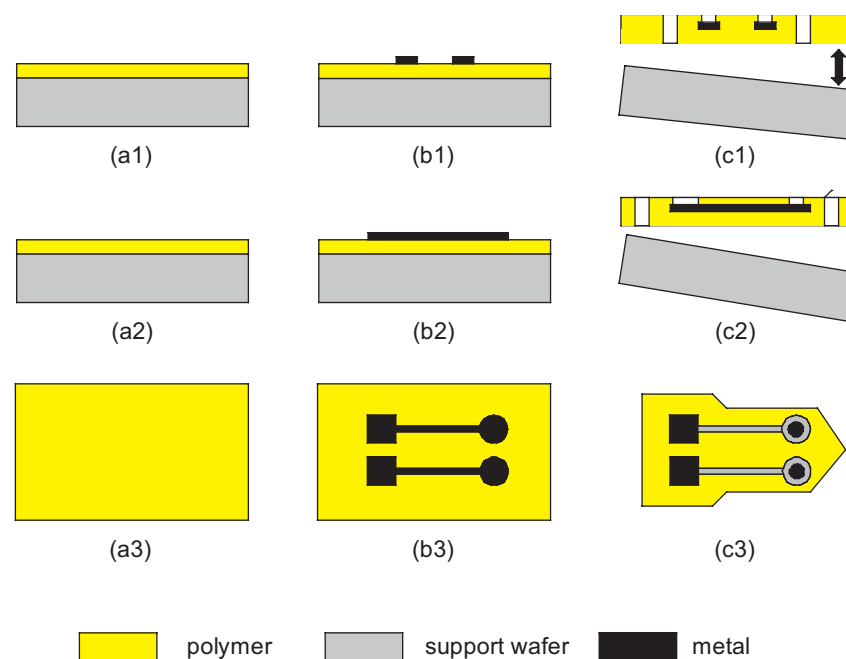


Figure 8. Schematic view of the fabrication of polymer based neural probes. Upper row: cross section; middle row: longitudinal section; lower row: top view. Dimensions are not in scale.

2.2 Manufacturing of microfluidic channels

Microfluidic channels are the key component for drug delivery and sampling of fluids. Depending on the intended use and the target specifications of the implant, manufacturing technologies have to be selected with respect to substrate material and specified channel dimensions. In principle, three different technologies to manufacture channels exist: bonding of two parts to form a channel, burying channels by digging a channel into a substrate and covering it again or surface techniques that form the channel on top of a substrate. These options have different advantages and disadvantages that will be discussed shortly after the introduction of the manufacturing technologies.

2.2.1 Bonding techniques for microfluidic channels

Bonding techniques for microfluidic channel manufacturing (Fig. 9) are applicable for silicon and for glass-silicon combinations as well as for polymer materials [44]. The channel is formed in most cases by a recess in one substrate that is bonded to a second one with a flat surface.

Both substrates can be preprocessed in a different manner which might be of importance if electronic circuitry is integrated in CMOS technology in one of it. The different bonding techniques are classified according to their physico-chemical principles.

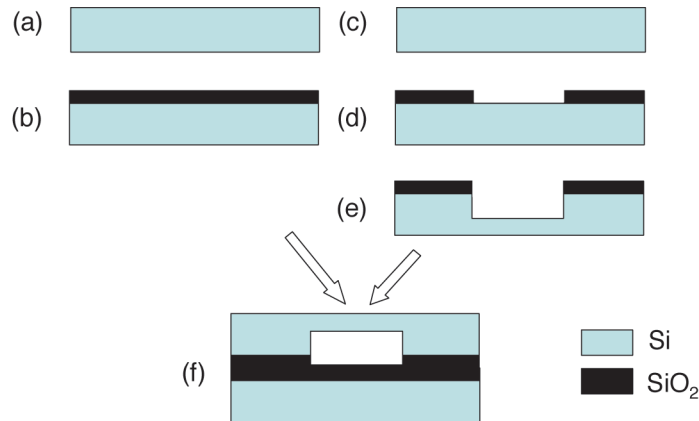


Figure 9. Fabrication of microchannels by wafer bonding.

Gluings

Two substrates are bonded together with the help of a polymer, e.g. SU-8 [45][46][47]. The polymer is deposited on (at least) one substrate. It is aligned and flipped onto the second substrate and both are pressed against each other. The polymer has to be hardened and/or cross linked under temperature of with UV light. The bond strength depends on the adhesion strength of the polymer to the substrate as well as on the cohesion strength of the polymer itself. Since the “glue” has to be sticky before the assembly there is always a hazard of channel obstruction by glue residues that are pressed into the channel during the hardening process. Compared to other joining techniques, gluing has the lowest bonding strength of all but can be applied with nearly all material combinations and at low temperatures.

Fusion Bonding

Direct bonding of silicon surfaces with silicon or silicon dioxide surfaces is called fusion bonding. Hydroxyl groups on the surface build a stable Si-O bond that cannot be released without destruction of the surfaces after the first contact. For a successful fusion bonding, surfaces must have a planar surface with a sufficiently large number of hydroxyl groups [48]. After alignment of the two substrates, the system is already stable but has to be tempered at about 1000 °C to reach the maximum bond strength [44]. This temperature is much too high for CMOS integrated circuitry and thereby not applicable to integrate channels into neural probes with monolithically integrated electronics.

Eutectic Bonding

Eutectic bonding takes place between a silicon surface and a metal alloy [49]. Gold (Au) is chosen in most cases as metal due to its stability and its eutectic temperature with silicon. The substrates are aligned and heated until they bond at the eutectic temperature. Mechanical stresses in the eutectic layer arise in large areas and cause breakage within the bond, this method is only applicable for small structures and areas, i.e. more on the device than on the wafer level assembly.

Anodic Bonding

Silicon or glass surfaces can be bonded to glass surfaces with means of anodic bonding [50][51]. After alignment on the wafer level, a voltage up to 1.2 kV is applied at a temperature between 300 °C and 500 °C. Thereby, alkali cations in the glass (e.g. Na) drift to the glass-silicon interface create a strong electrical field and help to produce a robust chemical bond. Temperatures are in a CMOS compatible range but high surface planarity is a prerequisite for successful bonding and high bonding strength. However, high electrical fields may cause collapse and destruction of channels [52].

2.2.2 Bulk micromachining for buried channels

Bulk micromachining is an established technology to manufacture buried channels in silicon based neural probes [53][54]. The silicon substrate is covered with a layer of silicon oxide that serves as an etching mask and lid of the channel at the same time (Fig. 10). The silicon oxide is structured with means of photolithography and dry etching with hole or grid like structures where microchannels shall be buried. Wet (Fig. 10 c) [53][54] or dry (Fig. 10e) [55][56] chemical etching is used to underetch the mask and create the channel structure. The geometrical shape depends on the chosen etching method. Wet etching is anisotropic according to the crystal structure of the silicon while dry etching is isotropic.

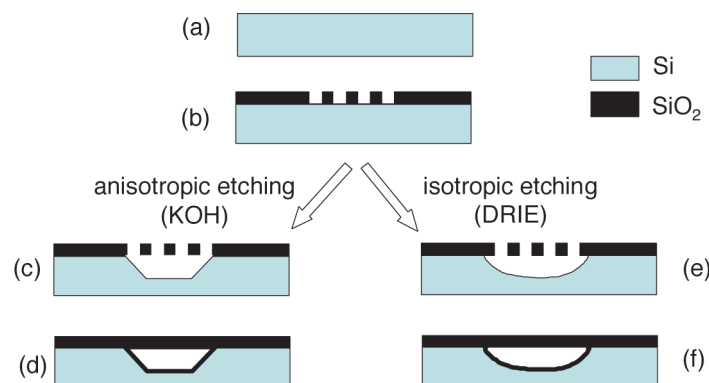


Figure 10. Fabrication of buried microchannels with silicon-based substrates.

In the last manufacturing step, the channels have to be closed. This is done by deposition of a passivation layer with means of chemical vapor deposition (CVD), silicon dioxide in most cases. Since the material deposits not only on the top layer and on the side walls of the openings but also diffuses through the openings in the top layer, a proper design of the dimensions of the top layer openings with respect to the channel dimensions is mandatory to obtain a closed lid over the channels before the channel is completely filled with the deposited passivation layer.

2.2.3 Surface micromachining for microfluidic channels

Surface micromachining allows the development of microfluidic channels with materials that might be different from the substrate wafer. Channel materials include metals [57], silicon [58], polyimide [59], parylene [60], and SU-8 [61]. The channel is either made with the help of a sacrificial layer or with a multiple exposures photolithography.

Fabrication technology that uses sacrificial layers for channel fabrication is quite simple (Fig. 11) and widespread. In a first step, a thin film is deposited either by spin coating or vapor deposition (Fig. 11a). The sacrificial layer that forms the channel is deposited and structured (Fig. 11b). Common materials for sacrificial layers are photo resists, degradable polymers like polyethylene glycol (PEG), aluminum or silicon dioxide depending on the channel material and the process technology that is used for probe manufacturing [62].

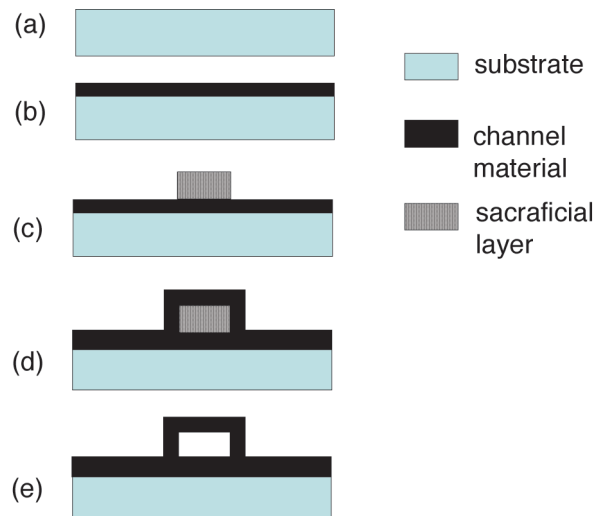


Figure 11. Fabrication of microchannels with a sacrificial layer based on polymer channel materials.

The top layer of the channel is deposited (Fig. 11 d) and the sacrificial layer is selectively removed. This removal has to be done by chemically dissolving the material out of the channel (Fig. 11e). According to the channel geometry with relatively small cross sections and long channel length, it takes a long time to dissolve all material. For successful use of the channels, bubble free filling is mandatory. In addition, the channel must stay stable before, during and after implantation in the brain. In a post process step, channels might be mechanically peeled of the wafer or released from the supporting substrate by a second sacrificial layer (not shown). Approaches with flexible wall materials have been combined with biocompatible and biodegradable substances like PEG [60] that degrade after implantation.

Multi exposure photolithography is an alternative method to generate microfluidic channels in photosensitive polymers like SU-8. Different methods have been developed to expose different areas with different doses of light to selectively polymerize the material and dissolve the non-polymerized parts. Using multi exposure lithography (Fig. 12) [63], a layer of SU-8 is spin coated on a substrate and exposed with to low dose of radiation that polymerizes only the top part of the layer (Fig. 12 a). In a second step, the exposure to a higher energy dose creates the side walls of the

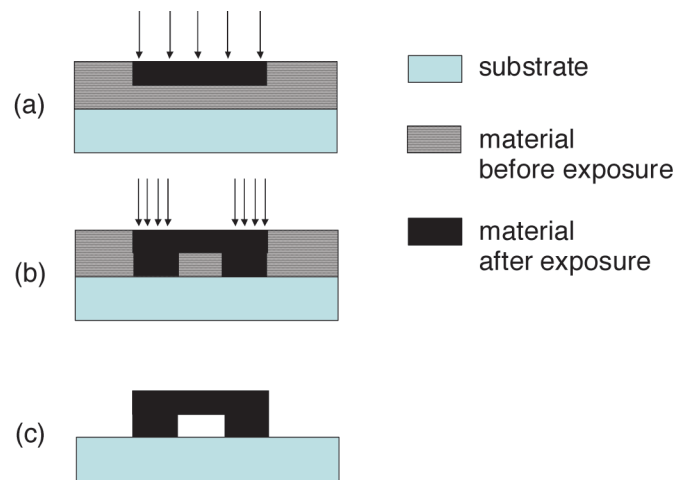


Figure 12. Fabrication of microchannels by multiple exposure of photosensitive polymer materials.

channel (Fig. 12 b). Dissolution of the non-polymerized material finally generates the channel structure

Another techniques to selectively expose different parts of a photosensitive polymer is the so called “moving mask” approach [64] in which the movement of a mask leads to exposure of different areas of the structure. The “buried mask” [65][66] uses a mask on a first layer of SU-8 to define the side walls and the channel. A second layer is spin coated on the mask and the channel lid is selectively exposed. Finally, the mask and the non polymerized polymer have to be removed by chemicals.

2.2.4 Comparison and assessment of technologies

The different technologies to manufacture microchannels have all their advantages and disadvantages. The bonding techniques allow a separate fabrication of the channel and the lid on separate wafers. Thereby, electrodes and integrated electronics might be processed in standard CMOS technology and only the lid wafer has to be manufactured with non standard processes. However, the assembly step is challenging and the lid wafer has to have via holes as outlets for the fluidic channels. This process step has been neglected to far in all presented processes. Buried channels require a complex process technology but only one wafer. The process delivers a flat surface and can be integrated into CMOS technology to monolithically integrate electronic circuitry. Surface channels can be made out of a large variety of materials with a theoretically simple process. In reality, the release of sacrificial layers and residual material is time consuming and limits the channel length and the length to cross section ratio. Due to their thin walls without further support from the bulk material the channels have a limited mechanical stability.

At the end, the choice of one technology will always be a trade over between different aspects of experience with one process and material or the other, the target specifications of the application and the preferences of the implanting neuroscientist with a certain type of neural probes.

2.3 Micromachined pumps and valves

Micromachined pumps and valves are the actuation parts that have to be integrated into a neural probe to generate an autonomous system out of a passive device. The field of micromachined pumps evolved over more than 30 years [67]. From the early day until today, there is still a constant development process with novel ideas and working principles. Especially the applications the life sciences where microfluidic channels and biosensors have to be integrated were a driving force over the last decades. Depending on the envisioned application, one has to carefully review the existing approaches. The emerging field of “lab on a chip” approaches has created reliable systems, often disposables, which are manufactured on a glass slide or out of silicone (polydimethylsiloxane: PDMS). They have reached large scale integration level and use soft lithography to reduce costs and allow fast production [68]. These systems are often designed to be used in a desktop device with external actuation “fingers” that drive membranes in PDMS and propel fluids through disposable chips. Valves are often realized by surface modifications of the chip and react to capillary forces or by pressure valves that obstruct the flexible PDMS channels.

If long-life implantable systems shall be developed other materials and working principles are durable materials are preferable. In micromachining, most micropumps are silicon based. For drug delivery applications, a closed valve in the off state of the pump is desirable to prevent drug leakage in a first failure of the implant.

Micropumps that can be classified by different properties of the pump:

- Type of flow
oscillating flow in “reciprogating micropumps” versus “continuous flow micropumps” [67].
- Pumping mechanism
mechanical versus non-mechanical displacement of the actuator [69][70][71]

Different physical and chemical actuation principles have been established to actuate fluids in micropumps (Fig. 13) [67][69][70][71]. Many of them are realized as reciprogating micropumps in

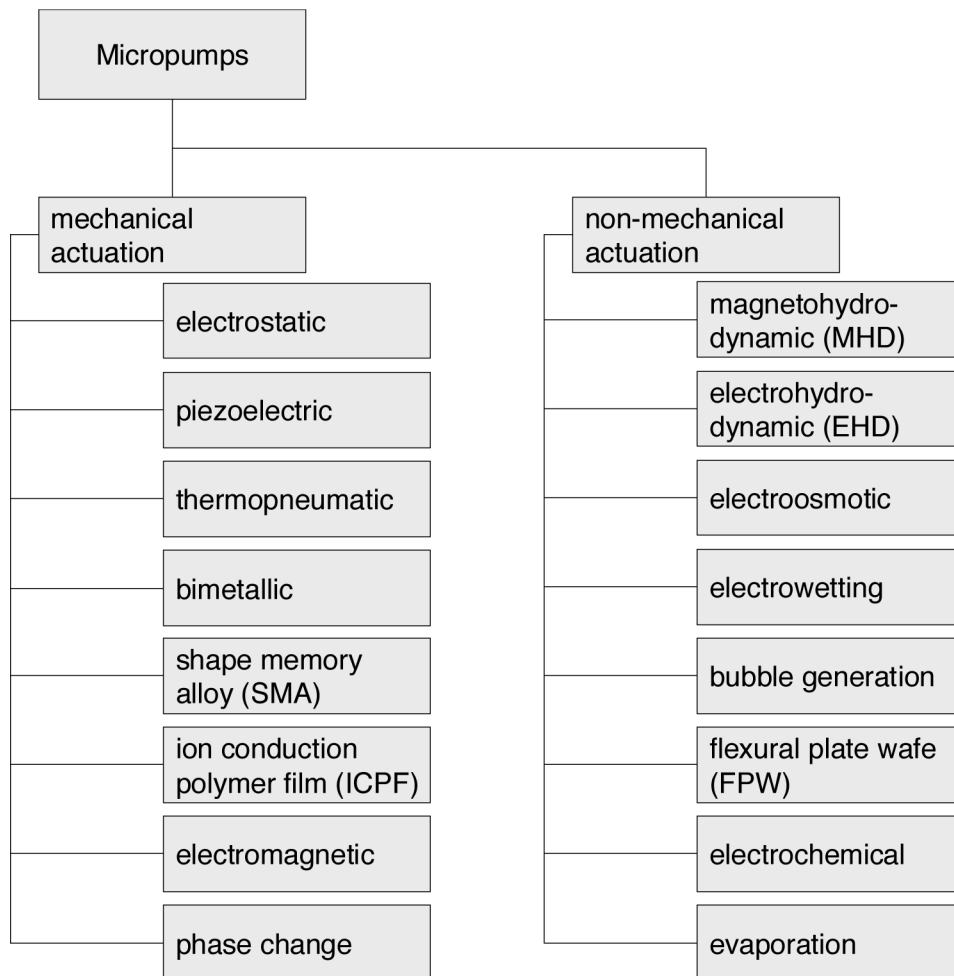


Figure 13. Classification of micropumps according to actuation mechanisms [71].

which an oscillating membrane actuates the fluid by movement of an elastic membrane (Fig. 14). Inlet and outlet valves promote unidirectional flow according to the desired flow direction. The pump works in two phases. In phase one, an underpressure is produced that blocks the outlet valve, opens the inlet valve and sucks fluid into the pump chamber. In phase two, overpressure is produced to block the inlet valve and pump the fluid through the outlet valve.

The realization of the micromachined pumps vary according to their actuation principle. If a reciprocating approach is used, the basic structures that are mainly built in silicon technology look similar in their basic components but differ in the details of the actuation unit (Fig. 15).

The diaphragm actuation mechanisms (see also Fig. 13) [70][71] decide about the driving voltages and energy supply as well as on the flow rates that can be achieved. The material properties of the materials, either silicon, glass, or polymers decide on the performance of the pumps as well as the actuation mechanisms. Depending on the materials and the manufacturing technologies (isotropic dry etching vs. anisotropic wet etching) different aspect ratios and feature sizes can be obtained. Valve design has to take adhesion forces of the materials into account as well as the Young's modulus of the valve materials to ensure proper opening and closure. Static valves are the simplest ones that have been established in the field. They are simple and reliable. Certain design rules have been developed to minimize the contact area between the substrates and the valves to minimize the opening forces. An overview is given in the cited reviews but goes far beyond the scope of this report.

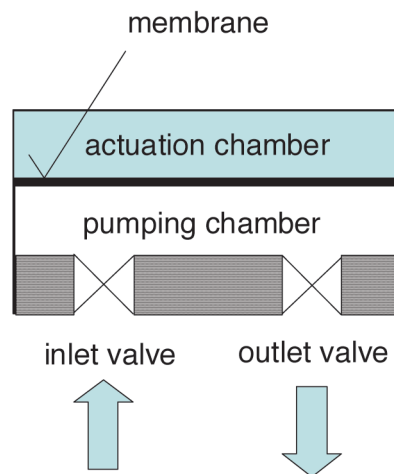


Figure 14. Working principle of a micropump.

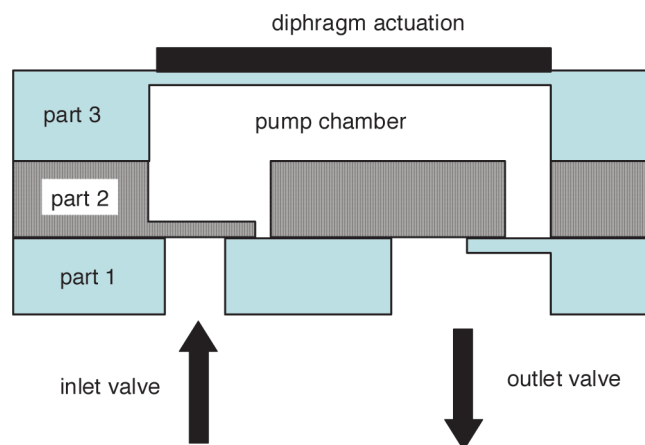


Figure 15. General working principle of MEMS based pumps.

Package size of the pumps goes hand in hand with maximum pressure and flow rate while the supply voltage depends on the actuation principle. However, voltages are often between tens and up to 1000 V when piezoelectric actuation is applied [72][71]. Shape memory alloys, conduction polymers and electromagnetic actuators allow lower voltages (1.5 V to 14 V) [70][72] but have lower pump frequencies than the high voltage actuators. Flow rates vary from the nanoliter to the milliliter range [69][71][72] and no general statements not simple guidance can be given.

A careful definition of target specifications like life time, flow rate, actuation speed, maximum package size and supply voltage has to be performed for every single application to chose from a variety of opportunities the most suitable one as a trade over of the different device properties. At the end, integration of the pump into an implantable system and connection to channels, tubing and reservoir decides about the success of the complete system.

2.4 Biosensor integration

The metabolic monitoring of the brain would give a deep insight of the biochemical processes that are related with physiologic and pathophysiologic processes. Especially in therapeutic applications, measurement of the neurotransmitters and chemical agents should be mandatory to control drug delivery in a closed-loop system according to the patient's needs.

Biosensor research has been conducted over decades, in many cases to monitor the blood glucose level [10]. In the brain, nitric oxide, dopamine, serotonin, GABA and glutamate are candidates of interest [9] but also glucose, lactate and acetylcholine [13] as already mentioned above. Different measurement paradigms and methods have been established that might be integrated into neural implants to monitor the metabolism of the brain. For in vivo recordings, the major challenges address the long-term stability, the detection limits and the biocompatibility, especially with respect to biofouling, i.e. protein adsorption on the sensor surface [11]. Microdialysis is one option to sample small volumes of fluid and analyze the agents of interest elsewhere. However, the temporal resolution is dependent on the detection limit of the substance and the flow rate of the dialysis [73]. Resolutions between 1 min. and 10 min. seem to be realistic but also strongly depend on the detection method with an extracorporeal device. More suitable are sensor principles that can be integrated on implantable probes. Amperometric sensors and cyclic voltammetry have been used to monitor in vivo the release of the transmitters as well as ATP (adenosine triphosphate), H_2O_2 , and adenosine [74]. The working principle of these sensors is based on an enzymatic layer for a specific transmitter that transforms the chemical interaction with the transmitter into an electrical signal during redox reactions [13][14][74]. The temporal resolution is also in the minute range. If amperometric sensors are used, calibration methods have to be considered since the sensitivity of these sensors often decreases due to a variety of processes including fouling processes at different sites and loss of enzyme activity. However, the development of microsensors and their integration into microprobes opens the door to measure neurotransmitters in vivo online [74]. The discussion about the use of amperometric sensors directly in implantable probes or in conjunction with microdialysis systems is ongoing [13][75] but shows the importance of these sensors in actual neuroscientific research.

3. CONCLUSIONS

Microsystem technologies have enabled the development of miniaturized devices for many applications. Especially in the field of implantable probes to interface nervous structures in the brain, this technology led to highly sophisticated microimplants. However, most of them have been only applied in fundamental neuroscientific investigation and the translation into clinical applications is a hard and long way. Even though technologies and components of electrodes and probes, microchannels and pumps are available, only few systems have been integrated microfluidic capabilities into neural implants [30][76]. However, pilot studies of neural implants integrated microfluidics show exciting opportunities. Intervention strategies to control tissue response after implantation seem to be feasible [77]. Injection of pharmaceutical agents does not harm the cells [78][26], if certain pressure limits are not exceeded. Together with the knowledge obtained from clinical applications of deep brain implants and vagal nerve stimulators, future perspectives look promising for multimodal neural implants. Better understanding of neuronal processes together with better diagnostic and therapeutic tools would be beneficial to the large portion of patients that suffer from neuronal diseases. However, a lot of detailed work on materials, components and their assembly, integration and packaging has to be done until these microimplants are ready to enter the market as active implantable medical devices.

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