Miniaturized Neural Interfaces and Implants in Neurological Rehabilitation

Thomas Stieglitz

Laboratory of Biomedical Microtechnology,
The Department of Microsystems Engineering-IMTEK,
The Bernstein Center Freiburg and the Cluster of Excellence
BrainLinks-BrainTools (ExC 1086),
Albert-Ludwig–University of Freiburg, Freiburg, Germany
stieglitz@imtek.uni-freiburg.de

Abstract. Restoration of functions after trauma or neurological diseases is the major goal of rehabilitation. Technical aids complement remaining functions or even try to replace them completely. Neural prostheses use electrical signals from the nervous system as control signals or excite nerves by means of electrical stimulation to elicit perceptions, induce movements or modulate neural network behavior. Creating novel, neural prostheses applications for the peripheral or central nervous system require neural interfaces and implants that are biocompatible, long-term stable and highly robust. However, only few neural interfaces have been tested or are routinely used in clinical applications today, most of them made with "old-style" precision mechanics technologies. What are the biological, tech- nological, electrical and material science challenges that must be considered when designing an optimal neural interface? Do nano-, micro- and biohybrid systems have a future in clinical applications of neural implants? Design aspects and opportunities and challenges of miniaturization technologies for neural implants will be presented and discussed for peripheral and central nervous system applications. Devices will be introduced and compared with respect to selectivity, long-term functionality and their applicability in funda- mental and translational research as well as for clinical applications.

Keywords: neural implant, rehabilitation, recording, stimulation, miniaturization.

1 Introduction

Neural prostheses aim to restore or replace lost functions due to trauma or neurological diseases. Since all neural functions in the human body come along with electrical activity of the nerve cells, the idea arose decades ago to take advantage of this property. Technical devices were invented to interface nervous structures to read out or to inscribe or even overwrite electrical information. Adequate interfaces are needed for this endeavor. They must

W. Jensen et al. (eds.), *Replace, Repair, Restore, Relieve – Bridging Clinical and Engineering Solutions in Neurorehabilitation*, Biosystems & Biorobotics 7,
DOI: 10.1007/978-3-319-08072-7_3,

neither harm the body nor lose their functionality over the course of the application. The earliest clinical application that replaced lost neural activity was the cardiac pacemaker. Its rise started in 1958 and it is the most successful active implant nowadays with more than 350,000 new implantations per year worldwide [1]. In neural prostheses or implants, only few success stories have been written so far. Cochlear implants to restore hearing have been implanted in about 250,000 patients worldwide. Deep brain stimulators to treat symptoms of Parkinson's (Lou Gehrig's) disease symptoms as well as vagal nerve and spinal cord stimulators modulate network activity by electrical stimulation very successfully [1]. Implants to activate ankle flexion after brain stroke, i.e. drop foot stimulators, and retinal vision prostheses have got medical device approval in the EC and the USA but are still far from market penetration. Recently, more applications have been developed in the field of stroke rehabilitation, epilepsy diagnosis and treatment, psychia- tric disease therapy, control of technical aids after para- lysis and artificial limbs after amputation to list the main research lines. Some of them are on the way into clinical practice, others still in different stages of fundamental research [1].

Further scientific findings are still needed to understand physiologic function and pathophysiological changes in many diseases to develop an "optimal" neural implant. On the other side, devices still look very "old-fashioned" or "vintage-style" in most clinical applications. Which target specifications have to be met to develop a new generation of neural interfaces and implants with modern miniaturization technologies ? Starting with a personal view on essential requirements of active implants, peripheral and central nervous system interfaces will be introduced. Chemical and optical interaction with the nervous system will be considered as alternative to established electrical recording and stimulation techniques. System concepts of implants that connect a kind of control center with its periphery conclude the overview.

2 Essential Requirements

Implants must not harm the target tissue and need to establish a long-term stable and functional interface. The technical term "biocompatibility" summarizes the main requirements that a device shall meet [2]. The used materials must not be toxic and shall interact with the tissue in a desired manner. Shape and mechanical material properties determine the structural biocompatibility that also influences the strength of the foreign body reaction. Implants will be encapsulated by electrically insulating tissue (either glia or fibroblasts) that deteriorates the recording and stimulation properties of the interfaces. Safety of the implant also includes material stability, the absence of eluates and debris and absence of tissue damage by (leakage) currents and electrical shock beyond the intended use. All these aspects have to be considered as fundament of application specific requirements.

3 Interfaces to the Nervous System

The intended use as well as the implantation site determines the design of neural interfaces. Invasiveness and selectivity in recording and stimulation have to be well balanced [3]. Miniaturization helps to interface with few nerve cells or axons but small electrode size results in increased noise and decreased charge injection. A compromise has to be found for every application. Suitable materials for implantable nerve interfaces include silicones, precious metals, polymers and silicon [4-6].

3.1 Peripheral Nerve Interfaces

Electrode arrays have to interface the axons, arranged in fascicles in the peripheral nervous system. For selective and graded recruitment, an electrode array is mandatory to be able to address several subgroups of nerve fibers. Electrodes can be wrapped around the nerve as cuff- electrodes or can be inserted either between or inside the nerve fascicles [3-5]. Designs differ in their designs according to electrode arrangement, shape, substrate and electrode material [3-5]; polyimide, parylene C and silicone rubber have been established as substrate materials while platinum, platinum iridium alloy, and iridium oxide are common electrode materials. Precision mechanics, laser structuring and microsystem technologies have been successfully applied to develop devices for clinical trials and approved devices. Microsystem based intrafascicular electrodes have shown highest selectivity in restoring natural sensory feedback in hand prosthesis control [7]. Long-term stability of the thin-film-based electrode contacts is of utmost importance [5] to transfer these promising approaches in clinical practice.

3.2 Central Nervous System Interfaces

Electrode arrays are either placed inside the cortex or deeper structures of the brain to record single unit activity or local field potentials or on or under the meninges of the brain. Shaft-like electrode arrays are preferred for intra-cortical implantations while planar arrays are suitable for epicortical application [6]. While fundamental researchers prefer stiff silicon-based arrays to record the activity of single nerve cells, chronic applications suffer from loss of active channels and signal due to encapsulation of these devices [6]. Reasons of this foreign body reaction include micromotions between the implant and the brain tissue. Flexible probes could be a solution. Further investigations are needed to prove reliability and long-term stability. In epicortical applications, increased electrode densities and numbers help to better understand mechanisms in the brain [8]. While polyimide-based microsystems [8] are success- ful in basic research, silicone rubber is taken for clinical research because of experience from other applications. Chronic stability and long-term functionality is the

limiting factor from the technical side. More complex probes might lead to better understanding of diseases and neural network activity that eventually leads to better probes.

3.3 Non-electrical Interfaces

Electrical activity in the nervous system is not only based on distribution of ions in the intra- and extracellular space but neurotransmitters influence nerve cell activity and synaptic transmission. Therefore, monitoring of the chemical environment, sometimes called metabolic monitoring, is of interest as well as local drug delivery [9]. Integration of microfluidic channels can be done technically but clogging due to protein and cell adhesion often limits the usefulness in chronic applications as well as the size of pumps, valves and reservoirs [9]. Opto- genetics takes advantage of the ability to genetically modify nerve cells and to obtain light sensitive ion channels. It allows novel investigation paradigms in basic research and needs adequate tools [10]. Microsystems engineering approaches are manifold to bring light to nerve cells and record the electrical response. So far, all developments are more or less in the prototype stage. Miniaturization, wireless communication and long-term stability are still major tasks on the agenda.

3.4 Tailoring the Material-Tissue Interface

Tailoring the material-tissue interface to either mimic the biological environment or to hide the technical substrate has a long history in implant development. Basic research is done on nanostructuring the surface, biochemical coatings, integration of cells onto or into coatings [11] and genetic engineering of coatings [12] to influence the tissue reaction after implantation. Most approaches, however, lack the ability to easily pass legal requirements in the context of medical device approval, e.g. with respect to sterilization.

4 Implant Concepts

The cardiac pacemaker and the cochlea implant have set standards with respect to reliability and robustness in (neural) implant concepts. They both protect implant electronics in a hermetic package against water and ions. Energy supply is either realized by a battery inside the package or a coil for wireless electromagnetic energy transmission inside or outside the package [13-14]. Non- hermetic packaging of electronic components can be done for preclinical studies or clinical studies with limited implantation time but might not be stable over decades [13]. Hermetic packages include a (limited) number of electrical feed-throughs that connect the electronic part inside with the electrodes outside. In approved medical devices this number of feed-throughs is limited to

about 20, so far. Current technology delivers packages at a certain size but has been able to deliver long-term stable systems that survive about 10 years even in parts of the body where motions are present [10]. Miniaturized implant packages have to face the challenge of integrating hundreds of electrical feed-throughs without deteriorating hermeticity. Ceramic-based packages in combination with Laser- structuring and micromachining deliver solutions for highly complex packages with predicted life-time exceed- ing human life expectancy. In addition, novel measurement and validation techniques have to be developed to over- come detection limits of established tests, e.g. the helium leakage test, when certain package volumes are underrun. The major challenge -according to the author's personal opinion- lies in the development of high channel-count connectors that allow reliable connection and detachment of the different components of an implant. If multiple electrodes with cables and an implant package with control electronics have to be implanted, detachable connections might reduce implantation trauma due to smaller incisions and tunnels. Single parts of an implant system might be replaced in case of failures and variability of implant components, e.g. lengths of cables, can be better adapted to the patient's needs. Commercially available solutions are limited to one, two, four and recently 8 channels for chronic implants. More sophisticated solutions are needed to be able to take advantage of microsystems solutions, of high channel count electrode arrays, and of complex system designs in chronic applications. Instead of connec- tors, multiple distributed implants with body area network communication to a central control implant can be envisioned as well as extracorporal receivers in a distri- buted network integrated in clothes (i.e. wearable elec- tronics). Intended use, application and patient numbers will influence the final design while the benefit to the patients' needs will determine the success of the implant in neural rehabilitation applications.

5 Conclusions

Miniaturization technologies enable highly complex designs for interfaces and implants in neural rehabilitation applications. Robustness and reliability of devices are of utmost importance as well as the benefit for the patient to bring exciting ideas into clinical applications. Long-term stability and functionality of neural implants are still major challenges, especially in miniaturized devices, that have to be solved before further success stories can be written.

Acknowledgment. Many parts of this work have been supported by German and European grants: Bernstein Center Neuro-technology-The hybrid brain (BMBF-01GQ0830), Cluster of Excellence BrainLinks-BrainTools (DFG, ExC 1086), Exist Go Bio (BMBF-01GQ0420), FutureRet (BMBF--16SV3792), BrainCon (BMBF-0316064C), NEURO- PROBES (FP 6, IST-027017), and TIME (FP 7, CP-FP-INFSO 224012). T.S. thanks P. Fries for continuous support and discussion on central nervous system implants.

References

[1] Stieglitz, T.: Neuroprothetik und Neuromodulation – Forschungs- ansätze und klinische Praxis bei Therapie und Rehabilitation. Bundesgesundheitsblatt-Gesundheitsforschung-Gesundheitsschutz 53(8), 783–790 (2010)
[2] Stieglitz, T., Schuettler, M.: Implant Interfaces. In: Hodgins, D., Inmann, A. (eds.) Intelligent Implantable Sensor Systems for Medical Applications, pp. 39–67. Woodhead Publishing Ltd., Cambridge (2013)
[3] Navarro, X., et al.: A Critical Review of Interfaces with the Peripheral Nervous System for the Control of Neuroprostheses ad Hybrid Bionic Systems. J. Periph. Nerv. Syst. 10(3), 229–258 (2005)
[4] Hassler, C., Boretius, T., Stieglitz, T.: Polymers for Neural Implants. J. Polymer Science-Part B: Polymer Physics 49(1), 18–33 (2011), Erratum in: 49, p. 255 (2011)
[5] Ordonez, J., et al.: Thin-films and microelectrode arrays for neuroprosthetics. MRS Bulletin 37(6), 590–598 (2012)
[6] Stieglitz, T., et al.: Brain-Computer Interfaces: An Overview of the Hardware to Record Neural Signals from the Cortex. Progr. Brain Res. 175, 297–315 (2009)
[7] Raspopovic, S., et al.: Restoring Natural Sensory Feedback in Real- Time Bidirectional Hand Prostheses. Sci. Transl. Med. 6(22), 222ra19 (2014)
[8] Bosman, C., et al.: Stimulus Selection through Selective Synchronization between Money Visual Areas. Neuron 75(5), 875–888 (2012)
[9] Stieglitz, T.: Integration of Microfluidic Capabilities into Micromachined Neural Implants. Int. J.of Micro-Nano Scale Transport 1(2), 139–158 (2010)
[10] Rubehn, B., et al.: A polymer-based microimplant for optogenetic applications: design and first in vivo study. Lab on a chip 13(4), 579–588 (2013)
[11] Stieglitz, T.: Restoration of Neurological Functions by Neuro- prosthetic Technologies: Future Prospects and Trends towards Micro-, Nano- and Biohybrid Systems. In: Sakas, D.E., Simpson, B., Krames, E. (eds.) Operative Neuromodulation. Acta Neurochir. Suppl., vol. 97(1), pp. 435–442. Springer, Wien (2007)
[12] Kim, Y.J., et al.: Genetically engineered bacteriophage delivers an anti-inflammatory peptide coating on neural electrodes. Biomed. Mat. 9, 015009 (2014)
[13] Stieglitz, T.: Manufacturing, Assembling and Packaging of Miniaturized Neural Implants. Microsystem Technol. 16(5), 723–734 (2010)
[14] Guiraud, D., et al.: An Implantable Neuroprostheses for Standing and Walking in Paraplegia: 5 Year Patient Follow Up. J. Neural Eng. 3(4), 268–275 (2006)
[15] Guiraud, et al.: Implanted functional electrical stimulation: case report of a paraplegic patient with complete SCI after 9 years. Journal of NeuroEngineering and Rehabilitation 11, 15 (2014)