FLEXIBLE, GRAPHENE-BASED ACTIVE IMPLANT FOR SPINAL CORD STIMULATION IN RODENTS

Andrada Iulia Velea[1,2], Sten Vollebregt[2], Vasiliki Giagka[1,3]

[1]*Bioelectronics Section and* [2]*Electronic Components, Technology and Materials Section, Department of Microelectronics, Delft University of Technology, Mekelweg 4, 2628 CD, Delft, The Netherlands*

[3]*Technologies for Bioelectronics Group, Department of System Integration and Interconnection Technologies, Fraunhofer Institute for Reliability and Microintegration IZM, Berlin, Germany*

E-mail: A.I.Velea@student.tudelft.nl

Abstract

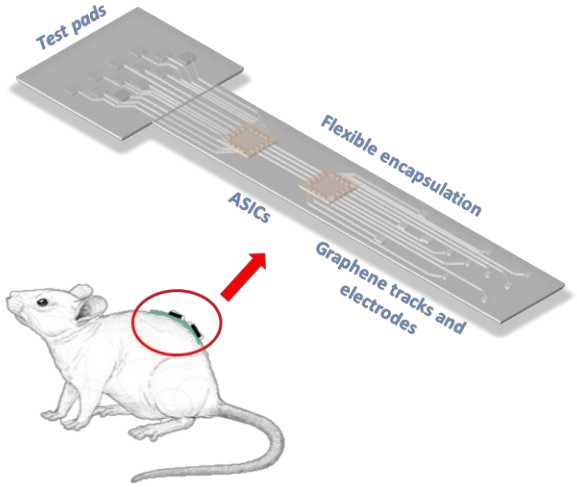
The most important symptoms of spinal cord injuries (SCIs) are partial or complete loss of sensory and/or motor functions caused by the disruption of the neural pathway between the brain and the extremities of the body. Recent studies have shown that epidural spinal cord stimulation (ESCS) can promote locomotor recovery in patients affected by SCIs, thus becoming one of the most promising means of treatment for the lesion.

Devices currently available on the market, consist of active components, enclosed in a hard case and connected via leads to the electrodes that form the interface between the stimulator and the biological tissue. The presence of leads along the spine, may be an important cause of failure for the device. Moreover, the overall stiffness of the stimulator does not resemble best the anatomical structure of the human body. Flexibility and optical monitoring of the biological tissue during implantation and stimulation are very important aspects and both can be improved with a proper choice of materials.

The goal of this work is to develop a compact, active, transparent and flexible spinal cord stimulator that could be implanted at the site of stimulation.

To provide high flexibility, soft encapsulation, using polydimethylsiloxane (PDMS) has been used. To ensure transparency but also mechanical stability of the electrodes and tracks, graphene has been chosen as a replacement for the conventional metals. Integrating active components, in the form of application specific integrated circuits (ASICs), on a graphene-based substrate, constitutes the biggest challenge. To this end, flip chip bonding techniques using a metal layer as an interface between graphene and the chip's stud-bumped pads, are being investigated.

Preliminary measurements after bonding have shown resistance values in the range of kΩ, thus taking the project one step closer to achieving the desired goal.



EMBEDDING SMALL AND THIN ELECTRONICS INTO FLEXIBLE IMPLANTS

Anna Pak[a,b], Wouter A. Serdijn[a], and Vasiliki Giagka[a,b]

[a]Bioelectronics Section, Department of Microelectronics, Faculty of Electrical Engineering, Mathematics and Computer Science, Delft University of Technology
Mekelweg 4, 2628 CD, Delft, The Netherlands
[b]Technologies for Bioelectronics Group, Department of System Integration and Interconnection Technologies, Fraunhofer Institute for Reliability and Microintegration IZM
Gustav-Meyer-Allee 25, 13355, Berlin, Germany

e-mail: A.Pak@tudelft.nl

Electronic components in the form of application-specific integrated circuits (ASICs) establishing the communication between the body and the implant, such as stimulation and recording, have, nowadays, become essential elements for current and future generations of implantable devices, as medicine is looking into substituting its traditional pharmaceuticals with electroceuticals, or bioelectronic medicines.[1]

Protection of implant components inside the body is a mandatory important step to ensure longevity and reliable performance of the device. The package of the implant should act as a bidirectional diffusion barrier protecting the electronics of the device from body liquids, and also preventing diffusion of toxic materials from the implant towards the tissue, at the same time matching tissue mechanical properties.

Current implants do not completely fulfil the desired properties mentioned above, facing different kinds of challenges. For soft implants made on polymer substrates and using polymer as an outer layer, encapsulation challenges happen at the interfaces of the polymer with other components inside the implant, as water ingress and condensation, which leads to electronics failure, happens there. In this work, an embedding process developed at Fraunhofer IZM[2] and used in semiconductor packaging field for chip encapsulation is being tailored to be used for protecting implantable ASICs. Such a method, which is based on a lamination process using heat and pressure, will reduce the critical interface points at the polymer-to-polymer contact due to the merging of polyurethane layers during the embedding process. Furthermore, flip chip bonding will allow to avoid long interconnects, as the interconnection bumps can be made on the whole chip area and redistributed on the polymer substrate.

In the proposed process, biocompatible polyurethane is employed and gold metallisation is used to form electrodes and connect them to extremely thin (10-30 µm) ASICs. The developed embedding process technology will ensure homogeneous distribution of mechanical stresses and longer reliability, resulting uninterrupted long-term use of smart implants (Fig.1).

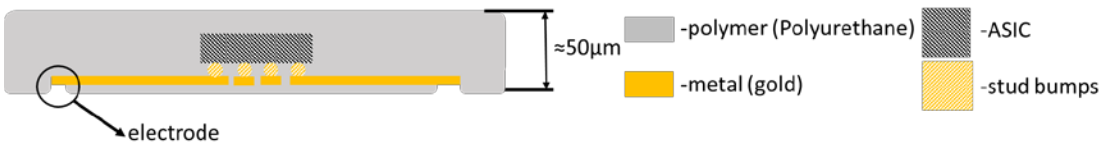


Fig.1. Schematic representation of embedded implant.

1. V. Giagka and W. Serdijn, "Realizing flexible bioelectronic medicines for accessing the peripheral nerves – technology considerations," Bioelectronic Medicine, vol. 4, no. 8, Jun. (2018).
2. A. Ostmann, A. Neumann et al. "Realization of a stackable package using chip in polymer technology," in Proc. 2nd Int. IEEE Conf. Polymers Adhesiv. Microelectron. Photon., pp. 160–164, Aug. (2002).

Towards a Semi-Flexible Parylene-Based Platform Technology for Active Implantable Medical Devices

Nasim Bakhshaee Babaroud[1], Marta Kluba[2], Ronald Dekker[2], Wouter Serdijn[1], Vasiliki Giagka[1,3]

[1]Bioelectronics Section and [2]Electronic Components, Technology and Materials Section,

Department of Microelectronics, Delft University of Technology, Mekelweg 4, 2628 CD, Delft, The Netherlands

[3]Technologies for Bioelectronics Group, Department of System Integration and Interconnection Technologies, Fraunhofer Institute for Reliability and Microintegration IZM, Berlin, Germany

E-mail: N.Bakhshaee@tudelft.nl

ABSTRACT

Active implantable medical devices have been developed for diagnosis, monitoring and treatment of large variety of neural disorders. Since the mechanical properties of these devices need to be matched to the tissue, soft materials are often preferred as a substrate.[1]

In this work we use a previously developed semi-flexible platform technology based on a parylene substrate and Pt metallization, for fabricating active implants in a monolithic process. [2] We use an IC fabrication-based platform that allows for the fabrication of several silicon-based rigid regions, which can serve as carriers for other components, connected to each other by means of flexible interconnects. According to Fig. 1, we aim to add more functionality to this technology and extend it to a platform for a variety of medical applications. We aim at assembling Application-Specific Integrated Circuits (ASICs) and co-fabricating other components for example, integrating Light Emitting Diodes (LEDs) or Capacitive Micromachined Ultrasound Transducers (CMUTs) for stimulation or wireless power transfer, to create multimodal implants.

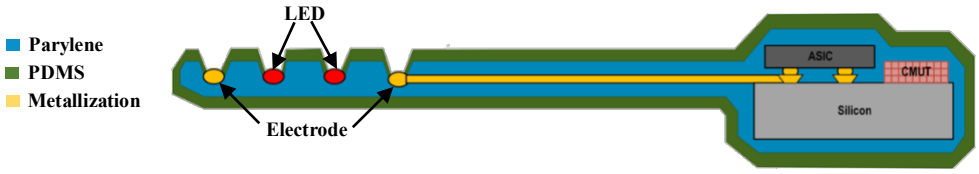


Fig. 1 Schematic of the semi flexible parylene-based platform

The platform is intended for chronic implants where the long-term reliability is critical. To this end, we intend to encapsulate our implant with an extra Polydimethylsiloxane (PDMS) layer.[3] Therefore, the current focus of this work is on enhancing the adhesion of PDMS to parylene, as it must remain strong for the required lifetime of the device. For this reason, thin ceramic layers are being investigated to improve the adhesion by making a chemical bond between these polymers, and also act as barrier layers for moisture penetration due to their higher molecular density compared to polymers. To characterize the adhesion strength, tape peel test and tensile test will be used before and after soaking the samples in saline solution.

REFERENCES

1. Hassler, C. & Boretius, T. & Stieglitz, T. Polymers for Neural Implants. *Journal of Polymer Science Part B: Polymer Physics*, 49, 1, 18–33 (2010).
2. Kluba, M. & Morana, B. & Savov, A. & van Zeijl, H. & Pandraud, G. & Dekker, R. Wafer-Scale Integration for Semi-Flexible Neural Implant Miniaturization. MDPI, 2, 13, 941 (2018).
3. Vanhoestenberghe, A. & Donaldson, N. Corrosion of silicon integrated circuits and lifetime predictions in implantable electronic devices. *Journal of Neural Engineering*, 10, 3 (2013).

Towards a flexible brain implant with 10.000 independent channels

Timothy Benjamin Hosman[1,2], Wouter Serdijn[1], Vasiliki Giagka[1,2]

[1]*Bioelectronics Section, Department of Microelectronics, Delft University of Technology, Mekelweg 4, 2628 CD, Delft, The Netherlands*
[2]*Technologies for Bioelectronics Group, Department of System Integration and Interconnection Technologies, Fraunhofer Institute for Reliability and Microintegration IZM, Berlin, Germany*
E-mail: tim.hosman@izm.fraunhofer.de

ABSTRACT

Electronic implants are becoming a valuable tool to explore as well as regulate neural activity, potentially overcoming neural disabilities that are not yet curable. For effective exploration and regulation, it has become increasingly necessary to cover larger areas of neural tissue and to interact at a higher resolution by means of electrode arrays. Application specific integrated circuits (ASICs) are often employed to accommodate the interaction with these electrodes but these are limited in size, which consequently limits the amount of individual recording or stimulation channels. The de facto solution that allows for the connection of an electrode array to an ASIC is to multiplex high numbers of electrodes to a single ASIC channel. However, due to switching and signal latencies only a limited number of electrodes can be multiplexed per channel. Multiple channels on an ASIC are therefore desirable to accommodate implants with a high electrode count.

Due to recent miniaturization advances, an ever-increasing number of channels can be made available on a single ASIC and the urgency arises to investigate technological complications of connecting these channels to electrodes. In this work we will investigate the technological complications of assembling a flexible electrode array substrate to an ASIC with a high number of independent channels. Our aim is to manufacture a biocompatible multi-layer substrate-ASIC assembly that can route 10.000 independent recording and/or stimulating sites to an array of electrodes covering a large area of the brain.

Monolithic Integration of an In-situ Smart Sensor in a Silicon-based Organ-on-a-chip Platform for Monitoring the Temperature of Stem Cell Culture

Ronaldo M. da Ponte[1], Vasiliki Giagka[1,2] and Wouter A. Serdijn[1]

[1] *Section Bioelectronics, Microelectronics Department, Delft University of Technology, Mekelweg 4, 2628 CD, Delft, The Netherlands*
[2]*Technologies for Bioelectronics Group, Department of System Integration and Interconnection Technologies, Fraunhofer Institute for Reliability and Microintegration IZM Gustav-Meyer-Allee 25, 13355, Berlin, Germany*

correspondence e-mail: r.martinsdaponte@tudelft.nl

This research reports on the design and co-fabrication of a time-mode signal-processing *in situ* temperature sensor customized for the Cytostrech, an organ-on-a-chip (OOC) device. The circuit was fabricated using an in-house integrated circuit technology (BiCMOS7) that requires only seven lithographic steps to fabricate npn and MOS devices, and is compatible with MEMS fabrication process. The technology was optimized to find the best trade-off between the the currrent gain (β_F) of the BJT and the current driving capacity of the MOS devices. The proposed circuit is developed to provide the first out-of-incubator real-time temperature monitoring of cell cultures on an OOC platform in a monolithic fabrication. The importance of this temperature monitorization stems from the fact that the temperature plays a pivotal role in the cell culture. As enzymatic activity and protein synthesis proceed optimally at 37.5 °C, a temperature rise can cause protein denaturation, whereas a drop in temperature can slow down catalysis and polypeptide initiation. The temperature setpoint of the incubator is controlled according to the temperature of its sensing element, which is not always the same what the cell culture is experiencing. On the other end, the cumulative effects of time spent outside the incubator can add up and greatly impact cell health. In fact, out-of-incubator temperature and its change over time are unknown variables to clinicians and researchers, while a considerable number of cell culture losses are attributed to this reason.
The system consists of two main blocks: a proportional to absolute temperature (PTAT) current generator (comprising of npn bipolar transistors to sense the temperature information) and a current-controlled relaxation oscillator.
Measurement results on wafer reveal a temperature measurement resolution of less than ±0.2 °C (3σ) and a maximum nonlinearity error of less than 0.3% across a temperature range from 25 °C to 100 °C.

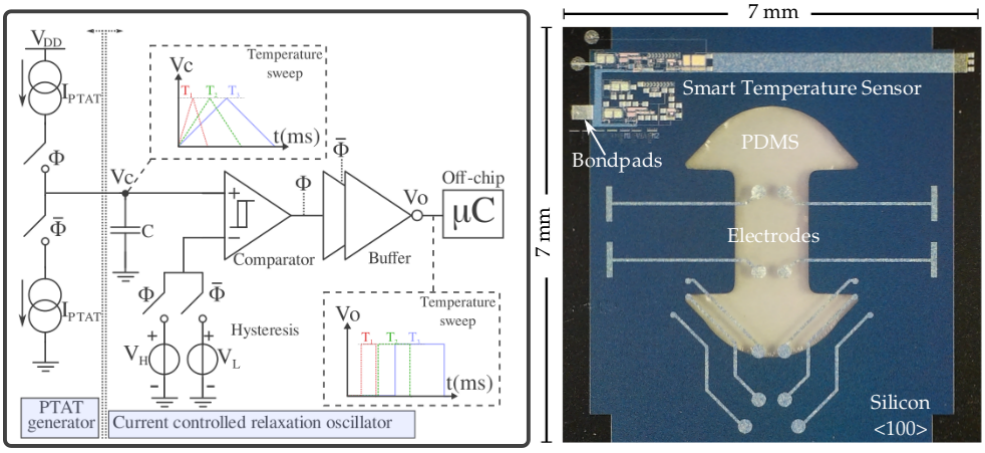


Figure 1: ***Left side:*** *System-level design detailing the main blocks: a PTAT generator and a current-controlled relaxation oscillator.* ***Right side:****The result of the MEMS-electronics co-fabricationusing the in-house EKL technology. A sheet of white paperwas placed beneath the chip to illustrate better the PDMS membrane area.*

DESIGN OF A MULTI-FUNCTIONAL SMART OPTRODE FOR ELECTROPHYSIOLOGY AND OPTOGENETICS

Ronaldo M. da Ponte[1], Chengyu Huang[1], Vasiliki Giagka[1,2] and Wouter A. Serdijn[1]

[1] Section Bioelectronics, Microelectronics Department, Delft University of Technology, Mekelweg 4, 2628 CD, Delft, The Netherlands
[2]Technologies for Bioelectronics Group, Department of System Integration and Interconnection Technologies, Fraunhofer Institute for Reliability and Microintegration IZM Gustav-Meyer-Allee 25, 13355, Berlin, Germany

correspondence e-mail: r.martinsdaponte@tudelft.nl

Optogenetics is a neuromodulation method that holds great potential for the realization of advanced neuroprostheses due to its precise spatial-temporal control of neuronal activity. The development of novel optogenetic implants (optrodes) may open new doors to investigate complex brain circuitry and chronical brain disorders, such as epilepsy, migraine, autism, Parkinson's disease, etc. Design challenges for the optrode include interference minimization between the µLED drivers and the recording electrodes, selection of proper materials, structures and dimensions to minimize tissue damage, biocompability, and batch production. In this work, we propose the construction of a multi-functional optrode to be used for physiological studies in group-housed, freely-moving rodents. It comprises commercial blue light µLEDs for optical stimulation, an active electrode array for recording the local field potentials at different depths in the brain. To accomplish this, silicon bulk micromachining is the essential technique used for the device manufacturing. Process steps include epitaxial growth, layers deposition, geometrical etching, ionic implantation, oxidation and diffusion. For the interconnection of the µLEDs, flip-chip bonding is used. The active microelectrode array (MEA) is constructed from a Ti/TiN layer to both meet the biocompatibility requirements and to reduce the electrode-tissue interface impedance, and by this the associated thermal noise. Finally, the optrode is coated with a PDMS film to electrically protect the µLEDs from the tissue and avoid uncontrollable electrical stimulation of the brain tissue.

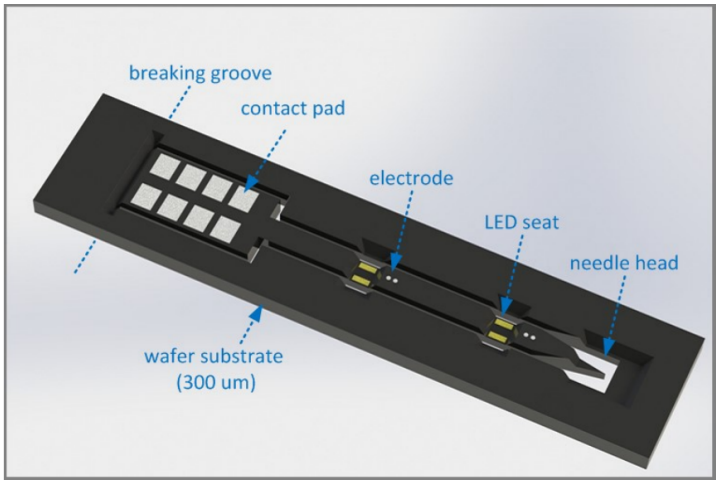


Figure 1: Illustration of the optrode (created with SolidWorks). Optrode's structure, record-ing sites, bonding pads and cavities for placing the µLEDs are depicted.

Title: Time and space-domain rakeness-based compressed sensing of atrial electrograms

Samprajani Rout [*] , Mauro Mangia [†] , Fabio Pareschi [¶†] , Gianluca Setti [¶†] , Riccardo Rovatti [‡†] , Wouter A. Serdijn [*]

[*]Section Bioelectronics, Delft University of Technology, The Netherlands;

[†]ARCES - University of Bologna, Italy; [¶] DET - Politecnico di Torino, Italy;

[‡]DEI - University of Bologna, Italy

Atrial electrograms (AEGs) acquired with a high spatio-temporal resolution are a promising approach for early detection of atrial fibrillation. Due to the high data rate, transmission of AEG signals is expensive in terms of power consumption and resources, making its adoption a challenge for low-power wireless devices. In this paper, we investigate the feasibility of using compressed sensing (CS) for the acquisition of AEGs while reducing redundant data without losing information. We apply two CS approaches, standard CS and rakeness-based CS (rak-CS) on a data set, composed of real medical recordings. We find that the AEGs are compressible in time, and, more interestingly, in the spatial domain. The performance of rak-CS is better than standard CS, especially at higher compression ratios (CR), both during sinus rhythm (SR) and atrial fibrillation (AF). The difference in the achieved average reconstruction signal-to-noise (ARSNR) in rak-CS and standard CS, for CR = 4.26, in the time domain is 7.7 dB and 2.6 dB for AF and SR, respectively. Multi-channel data is modeled as a multiple-measurement-vector problem and the mixed norm is used to exploit the group structure of the signals in the spatial domain to obtain improved reconstruction performance over l_{1} norm minimization. Using the mixed-norm recovery approach, for CR = 4.26, the difference in achieved ARSNR performance between rak-CS and standard CS is 5 dB and 2 dB for AF and SR, respectively.