CO-INTEGRATION OF FLIP-TIP PATCH CLAMP AND MICROELECTRODE ARRAYS FOR IN-VITRO RECORDING OF ELECTRICAL ACVITY OF CARDIAC CELLS

Asli Yelkenci, Ronaldo Martins da Ponte, Virgilio Valente

Department of Microelectronics, Delft University of Technology, Mekelweg 4, 2628 CD and Delft, The Netherlands, (A.Yelkenci@student.tudelft.nl)

The patch clamp is the golden standard to measure intracellular ionic activity of individual cells.[1] This technique, however, requires experienced personnel and results in a very low throughput of only a few cells per day. Microelectrode array (MEA) technology has been proposed as an alternative to study the excitable cells to perform multisite extra-cellular recordings, offering higher throughput and preventing micromanipulation on its setup. Although MEA can record the local field potentials (LPFs) which shows the average activities of multiple cells, they cannot detect the single excitatory/inhibitory subthreshold synaptic potentials.[2] Studies show that electrical properties of a single cell (membrane potential or ionic current activities) are essential to understand the complex and cooperative activity of multiple cells.[3] Concurrent high throughput patch clamp and MEA measurements are needed to gain insight in the correlation between single-cell intracellular activity and network dynamics in healthy and diseased cardiac cells.

In this abstract, we present a novel microfluidic system that integrates flip-tip planar patch clamps (FTPPCs) and (MEAs) on the same wafer, for in-vitro extra- and intra-cellular recordings of electrical activity of cardiac cells (cardiomyocytes).

Figure 1 shows a diagram of the proposed device. A silicon wafer is used for custom fabrication of the FTPPCs and MEAs. The FTPPCs (16 in total) are 15 µm in depth with a pitch between them of 400 µm to ensure that mechanical stability of the device. The planar MEAs (16 in total) are then patterned on the front side with 50 µm diameter and a pitch of 400 µm.

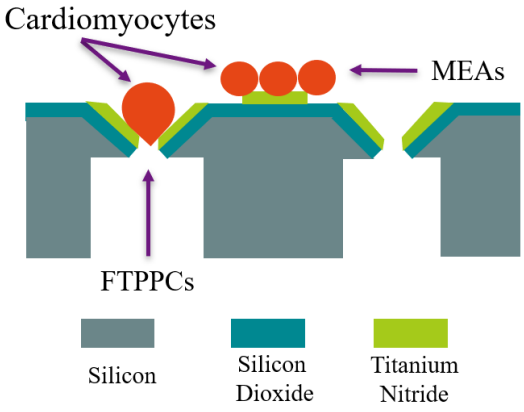

Fig. 1. FTPPCs and MEAs are built on the same wafer

The cells are trapped in the FTPPC apertures by ensuring that the gigaohm seal is achieved between the cell and FTPPCs. Intracellular recordings are performed by potentiostatic measurement. A 3-electrode configuration is used, in which the counter and reference electrodes are placed in the culture chamber (front-side) and one working electrode is in each suction chamber (back-side). LFPs are recorded from the MEAs using low-noise instrumentation amplifiers.

This abstract proposes a novel device that integrates both PPCs and MEAs on the same wafer. Co-integration of PPC and MEAs can provide valuable insight into the correlation between single-cell activity and cellular network dynamics of cardiomyocytes.

1. Spira, M. E., and Hai A. (2013). Multi-electrode array technologies for neuroscience and cardiology. *Nature Nanotechnology*, 8, pp. 83-94.
2. Hai A., Shappir, J., and Spira, M. E. (2010). In-cell recordings by extracellular microelectrodes. *Nature Methods*, 7(3), pp. 200-203.
3. Vardi, R., Goldental, A., Sardi, S., Sheinin, A., and Kanter, I. (2016). Simultaneous multi-patch-clamp and extracellular-array recordings: Single neuron reflects network activity. *Nature Scientific Reports*, 6, pp. 1-9.

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, such as polymers are often preferred as a substrate.[1] Parylene is a good candidate, as it is highly biocompatible and it can be deposited/etched using standard Integrated Circuit (IC) fabrication methods/processes. Further, the implantable devices should be smart, a goal that can be accomplished by including ICs. These ICs, often come in the form of additional pre-packaged components that are assembled on the implant in a heterogenous process. Such a hybrid integration, however, does not allow for size minimization, which is so critical in these applications, as otherwise the implants can cause severe damage to the tissue. On the other hand, it is essential that all components are properly packaged to prevent early failure due to moisture penetration.[2]

In this work we use a previously developed semi-flexible platform technology based on a Parylene substrate and Pt metallization, which allows integration of electronic components with a flexible substrate in a monolithic process.[3] We use an IC fabrication-based platform that allows for the fabrication of several rigid regions including Application-Specific Integrated Circuits (ASICs) and 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 thereby extend it to a platform for a variety of medical applications. An example of such functionality is integrating Light Emitting Diodes (LEDs) for optogenetic stimulation or integrating Capacitive Micromachined Ultrasound Transducers (CMUTs) for ultrasound stimulation or ultrasound wireless power transfer. Since the long-term reliability is critical for implantable devices, we intend to reinforce our implant with an extra Polydimethylsiloxane (PDMS) encapsulation layer that relies on the low viscosity of the uncured rubber to flow in every detail of the surface to prevent void formation.[4] Therefore, this work also focuses on enhancing the adhesion of PDMS to Parylene, as it must remain strong for the required lifetime of the device.

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

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. Giagka, V. & Serdijn, W.A. Realizing flexible bioelectronic medicines for accessing the peripheral nerves – technology considerations. *Bioelectronic Medicine*, 4, 1 (2018).
3. 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).
4. Vanhoestenberghe, A. & Donaldson, N. Corrosion of silicon integrated circuits and lifetime predictions in implantable electronic devices. *Journal of Neural Engineering*, 10, 3 (2013).

EMBEDDING SMALL ELECTRONIC COMPONENTS INTO TINY 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 the implant's outer layer should match the tissue's mechanical properties in order not to cause scar growth around the implant or damage the body.

Current implants do not completely fulfil the desired properties mentioned above, either lacking hermeticity or softness.

In this work, an embedding process developed at Fraunhofer IZM[2] and used in the semiconductor packaging field for chip encapsulation is proposed to be modified and used for protecting implantable ASICs. Such a method will have a number of advantages, such as miniaturization, in comparison with conventional titanium case packaging. Furthermore, embedding allows to avoid long interconnects, which can be a crucial problem for the device implanted inside a constantly moving body. The other advantage is that the geometry of these interconnects can be well controlled, and the amount of contact pads can be higher than in widely used wire bonding technology, because the distribution of solder bumps during embedding can take place on the whole chip area.

In the proposed process, biocompatible polymer materials will be employed to provide the implant with the required hermeticity and at the same time flexibility. The developed embedding process technology will ensure homogeneous distribution of mechanical stresses, resulting in high reliability for uninterrupted long-term use of smart implants (Fig.1).

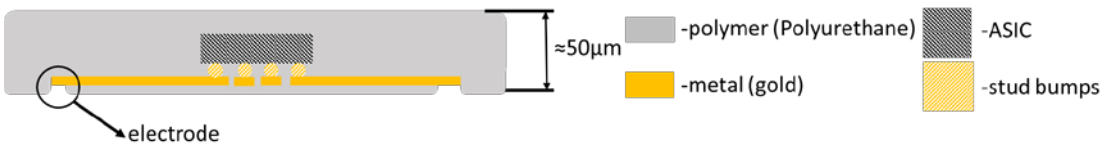

Fig.1. Schematic representation of embedded implant.

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).