5th Micro and Nano Flows Conference
Milan, Italy, 11-14 September 2016

Advancements in electrical-based techniques on chip for single-cell level analytics

Carlotta GUIDUCCI [1,*]

* Corresponding author: Tel.: ++41 (0)21 37813; Fax: ++41 (0)21 31105; Email: carlotta.guiducci@epfl.ch
1 Institute of Bioengineering and Institute of Electrical Engineering, Ecole polytechnique fédérale de Lausanne, CH

Keywords: Lab-on-chip, biosensors, microelectrodes, impedance flow-cytometry

Integrating biosensors and signal processing circuits will enable a new generation of biochips, providing addressing, measurement and elaboration functions on the same system. Potential applications for such multi-functional systems range from genetic arrays to personalized medicine-based tests, to cells manipulation and sensing. The main advantages of integrated electronics in biochip arrays have been shown in some recent successful applications. For instance, a fully-electronic system is now available for DNA sequencing [1], which enables fast read-out of large number sites and fluorescence-free protocols. In a different domain, researchers have demonstrated long-term observation of neural networks on chips integrating stimulation and elaboration circuitry and analog to digital conversion, providing fast sampling of low-amplitude signals from cells [2]. Moreover, in the framework of DNA analytics, we contributed to the development of the first fully-electronic integrated system for the label-free detection of DNA hybridization [3].

Major challenges in the development of biosensors on chip arise from reliability in a liquid environment. We contributed to the field by showing the superior performance of insulating material for surface passivation such as SU-8 and parylene and introducing new processing solutions for the enhanced stability of microelectrode features for electrical and electrochemical sensing on chip [4].

Integrated microelectrode technologies play a crucial role in lab-on-chip development since electric fields can be effectively used to sense, manipulate and move molecules and cells at the microscale. Nevertheless, high-throughput implementations of already assessed techniques are constrained by the design limitations entailed by planar electrodes in microfluidic configurations. These could be overcome by vertical electrodes, either integrated in micro-channel sidewalls or as free-standing structures. We proposed a new approach to achieve arrays of singularly-addressable vertical elements generating highly-confined electric fields for sensing or actuation [5 6]. Our approach is based on the conformal coating of passive cores with metal layers, defining electrodes in microfluidic channels with high aspect-ratio and vertical uniformity. This method achieves high electrodes density, granting high conductivity of both connections and metal sidewalls with no need for electroplating. The resulting vertical electrodes span the full height of the microfluidics, generating homogeneous fields along the z-axis of the channel.

Leveraging the technological advancement achieved, we are developing a label-free high-throughput on-chip systems for single-cell level discrimination and observation. In particular, we target the analysis of cells in flow, in a configuration where a large number of suspended cells flow through a chip and each cell is sampled by means of distributed non invasive sensors integrated in microchannels. Sensors have to be multiple and to be arranged in a wide channel to avoid clogging and cell damage by shear stress.

Our sensors can successfully discriminate cell types such as activated T cells, with the aim of identifying rare activated cells in human samples and isolate them for successive expansion. This system is presently based on two layers of metal and can be integrated with TSVs and IC for larger parallelism using the technology described in [7].

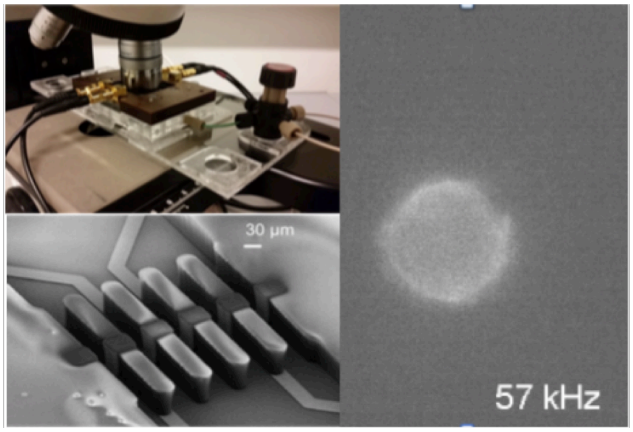

Figure 1. (Top left) Observation of single cells on the lab-on-chip system by high-resolution microscopy; (Right) Neuroblastoma cell observed on the chip during electrorotation experiments; (Bottom left): 3D microelectrodes integrated with microfluidics and SU-8 passive structures for impedance flow-cytometry.

References

1. Rothberg, J. M. *et al.* An integrated semiconductor device enabling non-optical genome sequencing. *Nature* **475,** 348–352 (2011).
2. Müller, J. *et al.* High-resolution CMOS MEA platform to study neurons at subcellular, cellular, and network levels. *Lab Chip* **15,** 2767–2780 (2015).
3. Stagni, C. *et al.* CMOS DNA Sensor Array With Integrated A/D Conversion Based on Label-Free Capacitance Measurement. *IEEE Journal of Solid-State Circuits* **41,** 2956–2964 (2006).
4. Temiz, Y., Ferretti, A., Leblebici, Y. & Guiducci, C. A comparative study on fabrication techniques for on-chip microelectrodes. *Lab Chip* **12,** 4920–4928 (2012).
5. Kilchenmann, S. C., Rollo, E., Bianchi, E. & Guiducci, C. Metal-coated silicon micropillars for freestanding 3D-electrode arrays in microchannels. *Sensors and Actuators, B: Chemical* **185,** 713–719 (2013).
6. Kilchenmann, S. C., Rollo, E., Maoddi, P. & Guiducci, C. Metal-Coated SU-8 Structures for High-Density 3-D Microelectrode Arrays. *J. Microelectromech. Syst.* 1–7 doi:10.1109/JMEMS.2016.2539000
7. Temiz, Y., Guiducci, C. & Leblebici, Y. Post-CMOS Processing and 3-D Integration Based on Dry-Film Lithography. *IEEE Trans. Compon., Packag. Manufact. Technol.* **3,** 1458–1466 (2013).