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Microfluidic device with integrated microelectrodes for enhanced EIS sensitivity

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Summary:
In this work a microfluidic device was created with nanostructured integrated platinum electrodes to enhance the sensitivity of Electrochemical Impedance Spectroscopy (EIS) in cell analytical applications. The sensing microelectrodes were structured using Focused Ion Beam milling creating two separate electrodes with gap sizes ranging from 200 nm to 1 µm. The decreased electrode distance allows improved sensitivity in EIS measurements, especially when a micrometer size particle or cell is trapped between the electrodes. The electrode design is supported by finite element modelling of the evolving electromagnetic field in the microfluidic channel.

Keywords: microfluidics, lab-on-a-chip, bioimpedance, electrochemical impedance spectroscopy

EIS measurements in cell analysis

In vitro study of individual cells or cell populations in a controlled chemical environment using specifically designed multifunctional microfluidic devices, such as Organ-on-Chips, offers sensitive and specific measurements that may facilitate drug discovery, screening, and the development of therapeutic strategies [1]. Combining these devices with integrated sensing systems, such as microelectrodes, can simultaneously maintain and monitor the behavior of cell populations real-time, meanwhile treating them with different chemical agents. This multidisciplinary approach can be essential in personalized medicine with further applications for antibiotic susceptibility testing [2].

Electrochemical Impedance Spectroscopy (EIS) is a non-invasive real-time technique that allows characterization of complex electrical properties of the cells while measuring the frequency dependent impedance of the system. Microelectrodes integrated inside a microfluidic system can be used for specific EIS measurements that enable cell analysis such as viability and growth monitoring. In biological applications of EIS an extensive range of frequencies is covered from 1 Hz to 10 GHz to get an insight into the inner electrochemical processes of the system regarding the electrode, the media, and the cellular properties as well. Accordingly, the spectra are divided into distinct dispersions regions α, β and γ [3]. Here, the α and β regions were measured to study both cellular and electrode properties.

Microfluidic system for EIS analysis

A compact multi-channel microfluidic system was created that can measure the EIS spectra of trapped cells using 2- or 4-electrodes architecture (Fig. 1). The central sensing microelectrodes were sectioned by Focused Ion Beam milling, creating two individual electrodes with a small gap ranging from 200 nm to 1 µm (Fig. 2). The system offers enhanced sensitivity owing to the nanometer scale electrode distances.

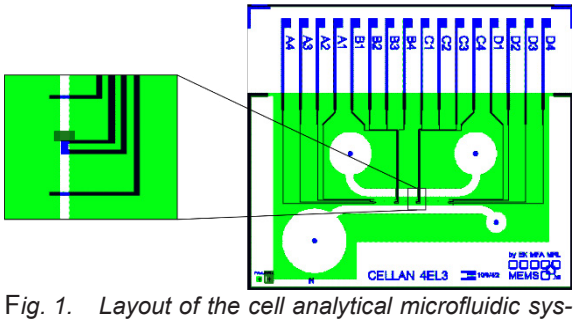
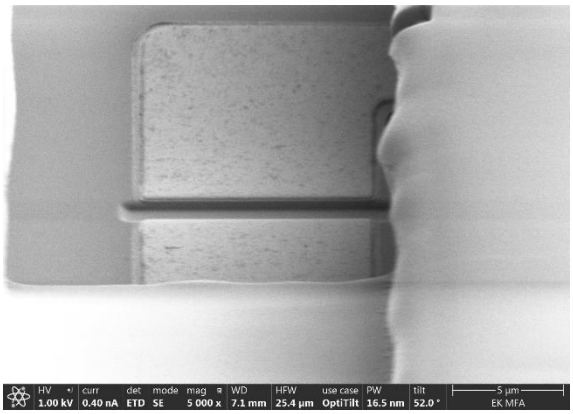


Fig. 1. Layout of the cell analytical microfluidic system and the position of the electrodes.



ig. 2. Sectioning the Pt electrodes with FIB milling. The gap size between the central electrodes is 1 µm.

Results

EIS measurements in 2-electrodes architecture were conducted using a PalmSens4 device, 4-electrode measurements were conducted by a bioimpedance analyzer developed by Vizvari et al. [4]. The Pt electrodes were fabricated on glass substrate, patterned by lift-off lithography. The microfluidic system contains two main inlet channels and 4 cross-channels for EIS measurements using the underlying electrodes. The cross-channels contain a trapping region, where cells or particles falling in the range of the channels' dimensions (e.g. yeast cells) can be localized over the sensing electrodes. The 10 µm deep microfluidic channels were fabricated in SU-8 by photolithography, then they were covered by a PDMS layer. The system is connected to the impedance spectroscopes via specifically designed PCBs (Fig. 3).

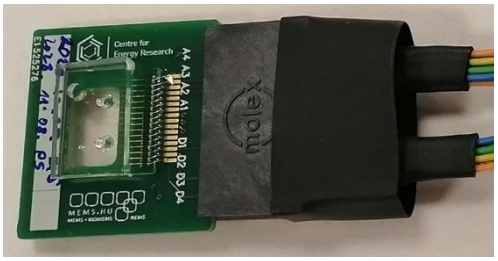


Fig. 3. The ready-to-use microfluidic device containing the cell trapping channels and the integrated electrodes.

During the measurements, the effects of the electrode distances, the stability and the reproducibility of the analytical system was characterized using different solutions, including cell culture media and cellular suspensions containing *Saccharomyces cerevisiae*. A finite element model was also developed to comprehend the electrical processes of the cellular system. The electric field developed in the channel was simulated by COMSOL Multiphysics with or without cells, the corresponding EIS spectra were compared to the corresponding measurements (Fig. 4). Initial tests with PBS, cell culture media (HEP G2) and cellular solutions yielded great reproducibility (Fig. 5). Comparison of 2- and 4-electrode measurements proved the benefit of using 4-electrodes in the low frequency range to eliminate parasitic effects.

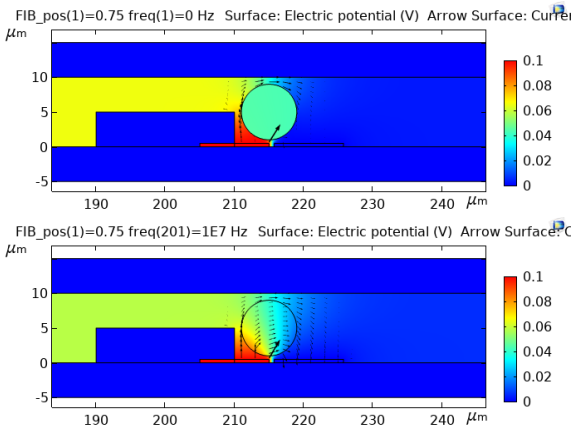


Fig. 4. FEM simulation of the electric filed over the electrodes when a cell is trapped at low (top) and high (bottom) frequencies.

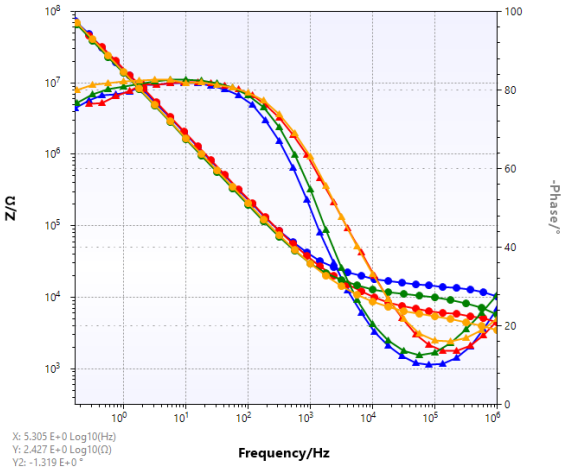


Fig. 5. Two electrode EIS spectra in PBS between two inner (red, yellow) and two outer electrodes (blue, green) in two different channels.

References

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