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Flexible microelectrode array based on PEDOT:PSS for neural recording and stimulation

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Summary. — Flexible microelectrode arrays placed on the surface of the brain cortex are promising tools for treating neurological deficits and restoring lost functionalities. Modern microfabrication techniques offer great possibilities to achieve high spatial and temporal resolution, but the device performances are ultimately determined by the material chosen as the biotic/abiotic interface. The conductive polymer poly(3,4-ethylenedioxythiophene) doped with polystyrene sulfonate (PEDOT:PSS) is a favorable material to use for this scope, due to its biocompatibility, long-term stability, and large charge injection capacity. Our research aims to realize an optimized device with flexible mechanical properties and low-impedance electrodes enabling efficient recording and stimulation of neural activity.

1. – Introduction

Neurological disorders account for 7% of the total global burden of diseases measured in disability-adjusted life years [1]. The social and economic impact of these diseases motivates technological advance and development in engineering, medicine, and material science. Neural interface technology aims to create a link between the outside world and the nervous system by stimulating or recording from neural tissue in order to assist people with neurological disabilities [2]. This two-way communication allows us to monitor the state of the brain and its composite networks and cells as well as to influence them to treat diseases or repair/restore sensory or motor functions [3]. Interfaces bridging biological systems and technology rely on simple physical stimuli such as ionic current pulses, mechanical vibrations or heating to trigger response at the cellular level. Conductive polymers (CPs) have been introduced in recent years to modify and replace the traditional inorganic materials for this purpose [4]. CPs such as poly(3,4-ethylenedioxythiophene) polystyrene sulfonate (PEDOT:PSS) combine a unique combination of properties such as

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high flexibility or even elastic behavior, swelling and soft mechanical properties, high ionic and electronic conductivities [5]. As a consequence, CPs mimic tissue-like properties and potentially offer improved bio-compatibility, reduced immune response and maximized signal to noise ratio [6]. In parallel, recent progress in microtechnology can provide novel concepts for directly linking the nervous system to external devices, but the fabrication of biocompatible electrodes with precise geometry and spacing, which is valuable for neuroscience studies, is still an open issue.

In this work, we face these challenges by developing and characterizing microelectrode arrays (MEAs) based on the conductive polymer PEDOT:PSS for electrocorticography (ECoG) experiments. We take advantage of microfabrication techniques onto flexible substrates to realize low-impedance devices both conformable with the brain surface and with high spatial and temporal resolution. We test the electrode arrays in an *in-vitro* setup combining electrochemical impedance spectroscopy (EIS), analysis of the voltage transients during simulated stimulation protocols, and atomic force microscopy (AFM) characterization of the PEDOT:PSS coating on the electrode surface. The combination of these techniques allows for the optimization of an implantable neural probe prototype potentially able to sense and stimulate the brain activity in chronic *in-vivo* experiments.

2. – Results

An optical image of the MEA resulting from the microfabrication procedure is presented in fig. 1(a). The flexible neural probe is composed of 32 independent recording and stimulating channels, allowing for conformability with the brain cortex and high spatial resolution in a small active area ($4.5\,\text{mm}^2$). An optical image and the detailed structure of a single electrode are reported in fig. 1(b) and (c), respectively. Titanium and gold metallic tracks are patterned onto a flexible plastic substrate (thickness $12.5\,\mu\text{m}$), and

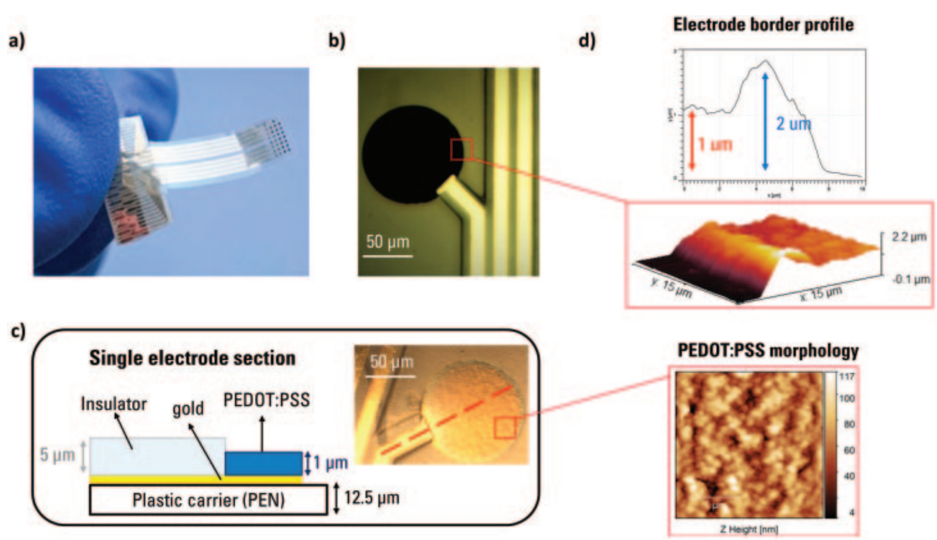

Fig. 1. – Microfabrication of the flexible microelectrode array. (a) Optical image of the neural probe. Picture (b) and structure (c) of a single electrode. (d) AFM topography of the PEDOT:PSS electrode coating, showing the electrode border profile and the morphology of the polymeric film.

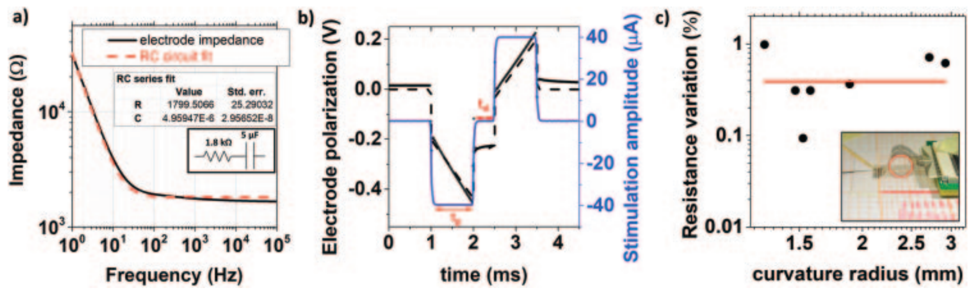

Fig. 2. – In vitro characterization of the flexible microelectrode array. (a) Electrochemical impedance spectroscopy of a single electrode, and fit with an equivalent RC circuit. (b) Electrode polarization during a stimulation procedure, and RC simulation of the voltage transients (dashed line). (c) Bending test on the neural probe, showing the variation of the resistance of a single electrode when the device is bent at different curvature radii.

insulated from the biological environment using a 5 μm thick negative photoresist, leaving only a circular electrode with diameter of 200 μm as the active region to be placed in direct contact with the brain surface. A 1 μm thick PEDOT:PSS layer is deposited onto the electrode surface to reduce the recording impedance and improve the device biocompatibility. AFM measurements on the electrode site (fig. 1(d)) provide the topography of the electrode border and the morphology of the PEDOT:PSS polymeric matrix. Results from the *in-vitro* characterization of the MEA are presented in fig. 2. The electrochemical impedance spectroscopy (EIS) (fig. 2(a)) of a single electrode was acquired in 0.1 M PBS solution, using an Ag/AgCl wire as the counter electrode. This can be modeled with an equivalent RC circuit description. In the high frequency regime, the electrode impedance is dominated by the electrolyte resistance R_{el}, and the large volumetric capacitance of PEDOT:PSS ($c_v = (45 \pm 5)\,\mathrm{F/cm^3}$)) limits the linear capacitive impedance increase in the low-frequency range. The electrode impedance at 1 kHz results to be 1.7 kΩ, indicating the low-impedance recording properties of the MEA. Figure 2(b) shows the electrode polarization during a typical neural stimulation protocol. Two current pulses (*phases*) with amplitude 40 μA and opposite sign are applied for $t_p = 1\,\mathrm{ms}$, with an interphase delay of $t_d = 500\,\mu\mathrm{s}$. The linear polarization transients indicate a capacitive charge injection from the electrode, and are accurately reproduced by an equivalent RC circuit simulation. Finally, we performed a bending test to study the impact of the mechanical deformation of the plastic substrate during practical use (fig. 2(c)). The MEA was bent at different curvature radii while measuring the electrical resistance of a single electrode with a micromanipulator needle (see inset in fig. 2(c)). Results highlight the large mechanical stability of the device, indicating how these two quantities are not directly correlated, with an average resistance change of 0.4% during the process.

3. – Conclusions

In this work, we develop and characterize a microelectrode array based on the conductive polymer PEDOT:PSS for neural recording and stimulation. We realize a flexible neural probe with 32 independent recording and stimulating channels. Electrochemical impedance spectroscopy measurements and the analysis of the voltage transients during simulated stimulation protocols demonstrate the low-impedance recording properties and the linear charge injection of the neural probe. The characterization of the bending properties of the electrode array highlights the device stability against mechanical deformation. These promising device properties originate from both the application of microfabrication techniques onto flexible substrates and from the use of conductive polymers as active materials. The neural probe will be interfaced with the Intan RHS system, featuring specialized integrated circuits for electrophysiology. We developed custom electronics with embedded stainless steel reference electrodes for chronic implantation. The final setup is expected to be an advanced platform to perform *in vivo* ECoG experiments.

4. – Experimental section

4˙1. *Microelectrode array fabrication.* – 12.5 μm thick polyethylene naphthalate (PEN) films (from Goodfellows) were fixed onto 2.5×2.5 cm glass carrier ($50 \times 25\,\text{mm}^2$) by using a thin polydimethylsiloxane (PDMS) layer. The Microposit S1818 positive photoresist was spin coated on the plastic foil (4000 rpm for 60 s) and annealed at 110 °C for 1 minute. Metallic contacts were patterned through direct laser lithography by using the ML3 Microwriter (from Durham Magneto Optics). The photoresist was developed with Microposit MF-319 developer. Then, 5 nm of titanium and 50 nm of gold were deposited by electron beam evaporation. Samples were immersed in acetone for 4 hours for photoresist lift-off. Metallic contacts were encapsulated with the mr-DWL 5 negative photoresist (from Micro Resist Technology). The resin was spin coated at 3000 rpm for 30 s and annealed at 100 °C for 2 minutes. After laser exposure, development was performed with mr-Dev 600 developer (Micro Resist Technology), and the resist was finally baked at 120 °C for 30 minutes. 1 μm of PEDOT:PSS was finally electropolymerized on the electrode surface through a two-electrode galvanostatic procedure ($I = 1\,\mu$A), starting from a solution containing 10 mM EDOT and 0.1 mM PSS in water, and using an Ag/AgCl wire as the counter-electrode.

4˙2. *Electrochemical measurements.* – Electrochemical measurements were acquired in 0.1 M PBS solution, using an Ag/AgCl wire as the counter electrode. Impedance measurements were performed with the MFLI lock-in amplifier (from Zurich Instruments), while the electrode polarization was measured with the Keysight 2912A source-measure unit.

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