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Microprinted, gold-based multiscale sensors for enhanced multimodal and label-free detection of bacterial resistance

Capteurs micro-imprimés multi-échelle pour la détection multimodale et sans marquage de la résistance bactérienne

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Chemical and biochemical analytics reach every aspect of our life from food quality control to disease diagnosis daily. Therefore, scientists are continuously pushing the limits of the techniques to better serve the needs of research communities and the public.

The aim of the phD work is to develop a rational design procedure to manufacture multimodal nanostructured microsensors to enable nanoanalytics via electrochemistry, Raman, and infrared spectroscopies, with enhanced detection limits. To demonstrate the capabilities of the new sensors, the phD student will address the challenging topic of antibiotics resistance evaluation through measuring biochemical changes in bacteria.

Electroanalytical techniques provide easy access to highly sensitive determination of electroactive species or electrical properties of various surfaces. Electrochemical sensors can be easily miniaturized to the microscale and be integrated into compact and multiplexed sensor arrays ideal for easy-to-handle portable devices. Engineering such micrometer-sized electrodes at the nanoscale, e.g., using gold nanoparticles, enables improving the electroactive surface for electron transfer efficiency, sensitivity, and response time[1]. However, these techniques are unable to provide molecular information and lack specificity for real sample analysis.
Spectroscopic techniques can provide structural information and can be used for chemical fingerprinting and identification. However, they often can't reach the sensitivity needed to detect very low concentrations and complex sample characterization. Vibrational spectroscopies, such as **Raman and infrared spectroscopy** suffer from these limitations, but their sensitivity can be strongly enhanced by plasmonic structures[2].

The combination of electroanalytical and spectroscopic techniques is ideal for exploiting high sensitivity and selectivity simultaneously. While narrow spectral-band surface enhanced IR spectroscopy and electrochemistry have been combined in the past[3] to the best of our knowledge, **no multimodal sensor was reported** that fully leverages the possibilities of plasmonic devices simultaneously for both vibrational spectroscopic techniques (IR and Raman) and electroanalysis. Development of such sensors will require multiple iterations between design and fabrication, which can be a slow and tedious process with lithography.

Additive manufacturing is an emerging technology with tremendous potential in industrial and health care applications. Beyond rapid prototyping, its share is continuously increasing in production. Among the various methods, **2-photon** induced **direct laser writing (2P-DLW)** has a prominent position because of its sub-micron resolution, originating from the 2-photon absorption process allowing strong laser excitation spatial confinement and subsequent chemical reactions even for the manufacturing of nanostructured metals[4]. These make 2P-DLW a perfect choice for the development of multimodal nanostructured

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microsensors as proposed. The sensors can be easily contacted as a part of electrochemical detection circuits as highly sensitive ultramicro-electrodes.

Combining electrochemical techniques with enhanced Raman and IR spectroscopies will enable to access not only to cell growth/disruption information (impedimetric analysis), but also to the cell membrane thickness and composition and electroactive/organic chemicals/enzymes released during the susceptibility testing (amperometry/IR/Raman).

Methodology

Individual sensor micro- and nanofabrication

The goal of this first part will be to develop the fabrication process of high-quality sensor structures in terms of micro, nano-structuring, and conductivity. Different approaches will be investigated to produce gold containing polymer microstructures of suitable conductivity.

Multi-modal sensor design

The sensor design and geometry will be adapted to answer to IR, Raman, and electrochemical detection requirements, taking advantage of the high resolution of the 2P-DLW technique to minimize electrochemical background signal, while ensuring sensitive spectroscopic response. Device structures will be assessed with SEM and AFM microscopies, concentrating on the nanostructure both in terms of the surface feature distribution and nanogaps, where strong electric fields will develop and help increase the detection limit. Highly sensitive impedimetric and amperometric responses will be targeted for electrochemical detection. SERS and IR enhancement will be assessed via Raman and FTIR microspectroscopy, respectively, and the measurements will be correlated with simulations and high-resolution structural information. The IR microspectroscopic and AFM studies will be conducted at the SMIS beamline of Soleil Synchrotron with the participation of F. Borondics (beamline manager).

Measurement cell and multi-modal sensor evaluation

A multi-modal measurement cell, in which the sensor chips can be inserted and microbial suspensions with antibiotics solution (few hundred µL) can be injected for drug testing will be produced. The cell will be designed to enable direct IR and Raman analysis after sample drying. Bacterial growth or lysis will be assessed by measuring impedimetric responses of sedimented cells after a given reaction time and comparing them with controls (without antibiotics). Raman and IR signatures of the cells, before and after addition of antibiotics, will be recorded after drying to provide information on the cell membrane and effect of antibiotics.

The research activity will be conducted both at ISA and at the Laboratoire de Chimie de l'ENS Lyon. The two institutes are not in the same campus, but they have good connection by public transport. Part of the experiments (IR microspectroscopy and AFM) will be performed in the Soleil synchrotron (Paris region).

Research profile:

The proposed work being highly multidisciplinary, several of the following skills are required: electrochemistry, analytical chemistry, basics of polymer chemistry, colloidal NP synthesis, vibrational spectroscopy, plasmonics and photochemistry.

A highly motivated and organized person with strong analytical thinking is expected.

References

[1] Sapountzi E et al, *Sens. Actuators B Chem* 238:392–401(2017); [2] Langer J et al, *Nano Lett.* 17:5768–5774 (2017); [3]Rosendhal SM et al, *Anal. Chem*. 85:8722–8727 (2013); [4]Arnoux C e t al, *Macromolecules* 53:9264–9278 (2020)