PhD Thesis. **Broadband terahertz spectrometry for molecular analysis of membrane permeabilization under oxidative stress conditions (M/F)**

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Selective control of cell membrane permeabilization is a major challenge in medicine (vaccines, cancer, etc.). We are studying the dynamics of membrane permeability using new tools in the terahertz spectral range, a promising field that has yet to be fully explored, on projects involving permeabilization triggered by therapeutic treatments. A major milestone has just been reached in photodynamic therapy (PDT), demonstrating the influence of drug formulation in micelle-type nanovectors on permeabilization, and a clear effect of their concentration [1]. However, this study was carried out at a single terahertz frequency. A spectroscopic study is therefore essential to enable an analysis of the nature of the permeating molecules. This is the aim of this project, using broadband terahertz spectroscopy over the 0.1-5 THz range, again in direct connection with the PDT vectors designed and produced in Toulouse, by developing a new wide spectrum terahertz sensor. Our teams have very recently described a major breakthrough in the use of terahertz spectroscopy for real-time monitoring of treatment-induced permeabilization [1].

The aim of the proposed project is to develop a broadband terahertz device, and to establish spectral mapping of cells subjected to relevant oxidative stress. The various cases addressed will be: sub-lethal photodynamic therapy which promises to be an effective strategy in the context of regenerative medicine, exposure to amyloid proteins in connection with neurodegenerative diseases, and exposure to polyionic complexes based on $Cu^{2+}$, an ion known for its involvement in oxidative processes. This thesis will draw on the complementary expertise of the Laboratoire d'Optique et Biosciences (Ecole polytechnique, UMR7645, Palaiseau): expertise in time-domain terahertz spectroscopy and sensors for biology, and the Laboratoire de Chimie des colloïdes, polymères & assemblages complexes (SoftMat, UMR5623, Toulouse): expertise in nanomedicine and oxidative stress related to photodynamic therapy and Alzheimer's disease. The thesis is based in Palaiseau, but a 9-month mobility in Toulouse is to be expected.

The candidate will develop new THz sensors at the LOB: optical design, construction and performance characterization. He or she will establish a database of THz spectra of solutes of biological interest. He or she will define the important parameters and implement a multi-zone, multispectral THz sensor enabling parallelized measurements on living cell biological samples. At SoftMat, the candidate will be trained in cell culture; familiarize himself/herself with polymer nanovectors used in sub-lethal PDT, already mastered and characterized in the laboratory; develop reliable and reproducible aggregation protocols for proteins involved in neurodegeneration (Aβ and Tau), taking advantage of SoftMat's recognized know-how in physico-chemical characterization; modify $Cu^{2+}$ HPICs to give them an elongated shape, quantify the cellular penetration of this object according to its morphology (ICP-MS) and measure its potential to produce oxidative stress. At the end of the PhD, the candidate will have carried out measurements on the cellular response to quantify the reaction dynamics under the effect of different oxidative stress promoters. From the THz dynamics obtained, and in particular the amplitude and characteristic time, a model of cellular behavior following these different oxidative stresses will be developed.

We are looking for a motivated candidate to develop this experimental project at the interface of physics and biology, with a solid knowledge of optics and optical spectroscopy. Additional experience in chemistry and/or biology is an advantage, but not essential. Basic knowledge of chemistry, biology or computer science (Matlab, Python) will be an additional asset. Candidates should send:

- a detailed CV
- a one-page cover letter
- the names and contact details of two referees
- grades from Master 1 and 2 or engineering school.

[1] Adv. Sci. 2023, 2300589.