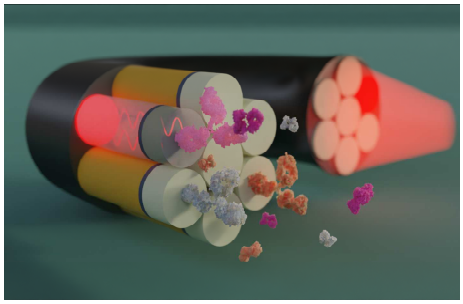
PhD proposal - financed by the GIMeD project OPALE (OPtique cérébrALE)



Artist's view of the developed biosensors

Title: "Development of optical fibers based biosensors dedicated to cerebral pathologies diagnosis"
Développement d'un dispositif de diagnostic sur fibre optique dédié aux pathologies cérébrales
Contact: elodie.bidal@univ-grenoble-alpes.fr
Co-supervisors: Gaëlle Offranc-Piret and Loïc Leroy
Start and duration of the thesis: October-November 2026, 36 months
Location: CEA, Grenoble, scientific polygon
https://www.cea.fr/Pages/le-cea/les-centres-cea/grenoble.aspx
Laboratories : SyMMES and BrainTech, https://www.symmes.fr/
Team: CREAB, https://www.symmes.fr/Pages/CREAB/Presentation.aspx
Required documents for candidates: CV, covering letter, recommendation letter(s)

Context:
The objective of the OPALE project, the context in which this thesis is situated, is to develop **novel optical fiber (OF) biosensors capable of performing multiplexed molecular analysis *in situ*, in real time and without labeling** intended to eventually replace biospies, which are time-consuming and invasive procedures. The field of application for such a tool is particularly relevant to the study of **brain diseases**. Since the evolution of cerebral diseases depends strongly on the environment of brain lesions, the ability to probe this environment and its evolution, inaccessible by conventional biopsy so far, may therefore prove very useful **allowing the monitoring of the pathologies evolution and prognosis, improving the precision of surgical margins and guiding the choice of local immunotherapy strategies** for example.

Based on our experience in plasmonic[1-3] and more recently in interferometric OF sensors[4,5], we propose to print **3D interferometric microstructures** at the end of each core of **a multicore OF** by 2 Photons Polymerization (2PP) process. These structures will then be gold-coated and functionalized with biological probes. The interaction of these probes with their targets will produce a change in interference, and measuring the intensity of the light reflected back at the functionalized end will provide information about the biological interactions occurring in these structures. Each core will act as an individual sensor, enabling **multiplexed detection (fig.1A)**. A preliminary work performed during the collaborative InSiBio project allowed to determine *ad hoc* composition and geometries of the microstructures to be printed at the end of the OF to confer them a sensitivity to the variations of refractive index. These results allowed to prepare different samples **(fig.1B)**.

Role of the PhD student:
Based on preliminary 2PP printing tests, the first interferometric structures will be printed by LIPhy at the very beginning of the project. The doctoral student will begin by observing these different samples by Scanning Electron Microscopy (SEM) imaging and characterizing their resolution and sensitivity to refractive index

variations. This characterization will allow her/him to familiarize herself/himself with the optical setup, which will first be adapted for infrared use, perform measurements (spectral analyses and intensity measurements), and process the associated data. These results will enable her/him to improve the structures by regularly sharing information with LIPhy.

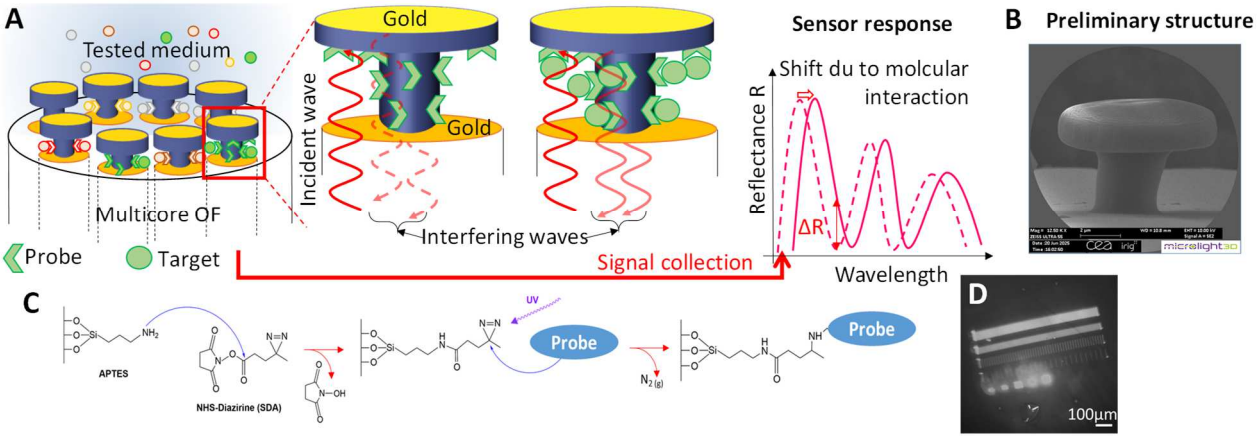


Figure 1 - A) Principle illustration, B) Preliminary 3D printed structure observed by SEM, C) Photo-functionalization protocol, D) Functionalized glass slide.

She/he will then work on developing protocols to functionalize the ends of the OF in several distinct areas with diameters of approximately 100µm². She/he will begin by adapting the existing photo-chemistry protocol (fig1.C,D) to resin microstructures printed on flat surfaces. The doctoral student will focus on both optical aspects (optical assembly, UV illumination) and surface chemistry (preparation and grafting of receptors). She/he will, of course, be supported by the physicists and biochemists of the CREAB team in order to advance this development, which will constitute an important part of his/her thesis.

The other important part will concern the biological validation of the sensor. Once functionalized, it will have to demonstrate its multi-detection capabilities. To do this, the doctoral student will have to detect several biological targets in increasingly complex and "solid" environments. Robust passivation methods will need to be implemented to avoid non-specific detections or even gradual passivation of the sensor. Detection environments will gradually be brought closer to real environments, with the ultimate goal of multiplexed detection of biomarkers of interest in a brain tissue model. The doctoral student will be supported in this task by the BrainTech Lab.

The thesis will be jointly supervised by SyMMES and BrainTech.

Skills developed:

During this thesis, the doctoral student will acquire or strengthen her/his skills in optical instrumentation, theoretical optics, image processing, surface chemistry, and biochemistry in the highly multidisciplinary context of biosensors.

References:

[1] Vindas, K., *et al. Enhanced sensitivity of plasmonic optical fiber sensors by analyzing the distribution of the optical modes intensity.* (2020) Optics Express doi.org/10.1364/OE.399856

[2] Desmet, C., *et al. Multiplexed Remote SPR Detection of Biological Interactions through Optical Fiber Bundles.* (2020) Sensors, MDPI doi.org/10.3390/s20020511

[3] Vindas, K., *et al. Highly-Parallel Remote SPR Detection of DNA Hybridization by Micropillar Optical Arrays*. (2019) Analytical and Bioanalytical Chemistry doi.org/10.1007/s00216-019-01689-2

[4] Bratash, O., et al., *Multiplexed bio-detection on an interferometric optical waveguide assembly.* (2025) Advanced Materials Interfaces https://doi.org/10.1002/admi.202400941

[5] Bratash, O., et al., *Optical fiber biosensors toward in vivo detection.* (2024) Biosensos & Bioelectronics. https://doi.org/10.1016/j.bios.2024.116088