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INTERNSHIP PROPOSAL:

SIMULATION AND INVERSE PROBLEM

applied to molecular oligomerization

The organization of biomolecules into macromolecular and supramolecular complexes is crucial in many functions of living cells. Oligomerization, clustering and aggregation mediate a myriad of biochemical processes. For example, in cellular signaling, the same molecule can modulate its affinity to its partners and activate different cellular response depending on whether it is in monomeric or oligomeric states. Hence, measuring the presence and distribution of these oligomers is an important challenge.

This project is focused on the use fluorescence fluctuations based methods to answer this question. This family of methods, derived from Fluorescence Correlation Spectroscopy (FCS), makes it possible to measure molecular concentration and mobility in living cells by analyzing the signal fluctuations caused by fluorescent molecules (or molecular complexes) as they diffuse across a small observation volume. This observation volume is typically created at the focus of the objective lens in a confocal microscope. FCS has been used to probe molecular aggregation before. However its output is usually limited to an average value of brightness (photon rate emitted per molecular complex), which, if it is higher than for monomers, indicates the presence of oligomers, but it does not provide the size distribution of these oligomers. We propose to use photobleaching as an extra control parameter to recover this size distribution: indeed, the variation of brightness as more and more fluorophores are bleached depends on the oligomer size. Hence this project aims at finding a method to extract the size distribution of a mixture of oligomers from the distribution of photon counts recorded at various stage of photobleaching.

In a first step, computer simulations will be performed to obtain fluorescence fluctuation measurements from a mixture of oligomers. Then the results of these simulations will be used to solve the inverse problem using an optimization approach. In collaboration with biologists from Institute for Advanced Biosciences (IAB, Grenoble), this method will be applied to Cry2, a photoconvertible protein, that has the ability to oligomerize under blue light illumination, and is a wide-spread molecular tool for optogenetics.

We are looking for a student with a background in physics or signal processing and an interest for working in a multi-disciplinary environment. Knowledge in optimization methods and inverse problems would be an asset. The internship will take place in an interdisciplinary team with people specialized in physics, optics and biology.

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