COFUND-Project: Multiscale approaches to investigate the conformational landscape of flexible protein assemblies: Deciphering the NADPH oxidase complex

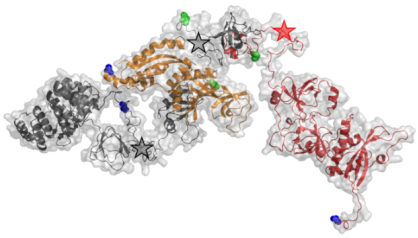
2 years postdoctoral position at the Theoretical Biochemistry Laboratory,
Institut de Biologie Physico-Chimique, 13 rue Pierre et Marie Curie, Paris France

Lead PI: Dr Sophie Sacquin-Mora (sacquin@ibpc.fr)/ CNRS UPR 9080 / Theoretical Biochemistry Laboratory
Co-PI: Dr Antoine Taly (taly@ibpc.fr)/ CNRS UPR 9080 / Theoretical Biochemistry Laboratory

Short description

Numerous proteins contain **intrinsically disordered regions** (IDRs) which challenge the classical structure-function paradigm. Instead of adopting structured folds, IDRs are better described using conformational ensembles and their investigation at the molecular level has been a central challenge in structural biology.

IDRs are involved in an increasing number of physio-pathological situations. This project focuses on an attractive therapeutic target, the phagocyte NAPDH oxidase (NOX) complex. This complex is among the most important sources of ROS (Reactive Oxygen Species) in living organisms and present in many cell types. ROS production is a major mechanism of microbial killing by phagocytic immune cells. The balance between pathogen killing and chronic inflammation is controlled by the regulation of the oxidase from the resting to the active state. This regulation induces changes in the subcellular localization, the conformations and the interactions of the 6 proteins involved in the complex: 2 membrane proteins, NOX2 and p22, the cytosolic subunits p40, p47 and p67, and the small GTPase Rac. The Cterm of NOX2 as well as p47 and p67 contain structured domains separated by IDRs. Their flexibility is central for their activity. The identification of the molecular events that trigger the assembly of the oxidase at the membrane is a challenge for cell biology, biochemistry and host-pathogen interactions. These events are also critical in the search for pharmacological modulators that is actively pursued by several drug companies to limit inflammation.



Upon activation, the cytosolic complex moves to the cell membrane and activates an electron transfer chain within NOX2. Several interactions between the cytosolic subunits, the membrane proteins NOX2 / p22 and the lipids have been identified using FRET experiments in the research group of Pr. Marie Érard and Pr. Oliver Nüsse (Institut de Chimie Physique, CNRS-U.Paris-Saclay), thus leading to strong geometrical constrains during the activation steps.

In order to understand how the cytosolic complex can adapt to those constrains, we want to improve its 3D modeling by also investigating the **dynamic properties of the complex**. This will require to take in account the various conformations potentially adopted by the unstructured regions. This involves the elaboration of a new computational strategy adapted to the modeling of proteins composed of structured domains separated by flexible segments with two successive computational steps:

- Using Molecular Dynamics (MD) simulations to generate relevant conformational ensembles for the flexible linkers connecting the complex structured domains. This will require the use of state of the art force fields, that are suitable for modeling both structured and disordered protein regions.

- Investigating the interactions between the structured domains with an integrative docking strategy (using both coarse-grain and all-atom representation levels), that will take into account structural constraints produced by the MD simulations on the linkers and experimental data from our experimental partners.

In addition, this second step will enable to identify residues that likely to play a key part in the cytosolic complex, and these residues will represent preferential targets when trying to modulate the complex activity with point mutations.

Practical information:

Qualifications: The candidate should hold a PhD in Computational chemistry of physics or Bioinformatics, with a strong background in modeling of biomolecular systems. Experience in classic modeling tools such as Molecular Dynamics or Docking is expected. Excellent communication skills in English, both verbal and written, are required. The thesis should have been defended less than 2 years before the start of the postdoc.

When ? The deadline for sending the application is October 31st, 2021. The candidate should be available for starting the postdoc between March and July 2022.

How to apply: Applications should be sent to **dynamoCofund@ibpc.fr** as early as possible and **before october 31st 2021**. The application should include:

- a detailed Curriculum Vitae, including a transcript of PhD diploma
- 2 recommandation letters
- a motivation letter describing why you should be considered for this position.

It is highly recommended for the candidate to first contact he lead PI and co-PI of the project to assess the suitability of their application before applying.