INSTITUT DES SCIENCES ANALYTIQUES

Development of new models for the study of dynamics and interaction of multidomain proteins.

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Développement de nouveaux modèles pour l'étude de la dynamique et des interactions des protéines multi-domaines.

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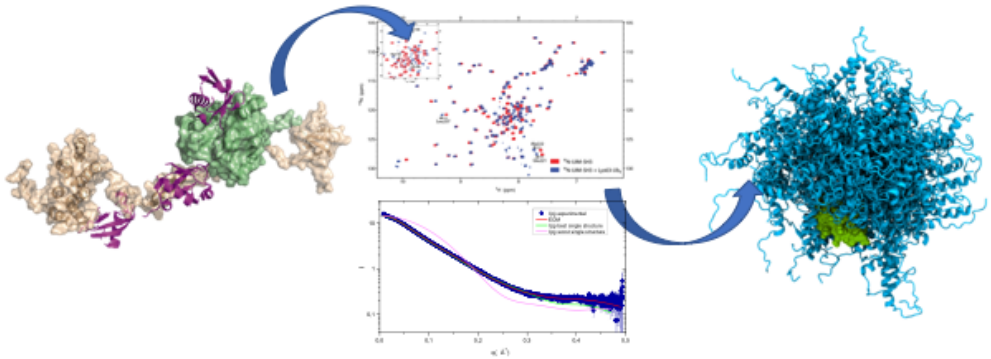
Since more than three decades, the structure of proteins has represented a powerful paradigm for the study of their function. It has led to an impressive number of structures of folded proteins and fundamental advances in our understanding of protein association. Yet, pioneering studies on intrinsically disordered proteins (IDP) or protein segments (IDS) have revealed that neither the organization in structured folds nor the establishment of stable interactions are always necessary for association involving IDPs or IDSs to take place. These phenomena are highly heterogeneous, ranging from stable interactions resulting from disorder to order transitions, to fuzzy interactions involving conformational ensembles or clouds. Furthermore, multidomain proteins can simultaneously present well folded domains and highly flexible linkers. In such a case, these linkers enable interface remodeling in response of a variety of partners. Disordered proteins (Intrinsically Disordered Proteins, IDPs) or protein segments (intrinsically disordered segment, IDSs) are now recognized as key players in the cell machinery, notably as mediator or modulator of macromolecule interactions or as signaling hubs. This opens a new area of research where the classical structure-function approach does not hold anymore. Defining a new paradigm to understand the function of IDPs in the cell necessitates revisiting the way interactions are characterized and identifying relevant descriptors linked to function.



The present thesis project aims at developing and using different techniques to understand the role of IDS in their interaction with several partners. Moreover, new models will be developed to better understand the dynamics of multidomain proteins. The techniques will mainly concern NMR but also SAXS/SANS and a possible collaboration with physicists of the "Institut Lumière Matière" to deal with ion mobility mass spectroscopy (IMS). These biophysical techniques will be complemented by molecular dynamics simulation and the programming of new dynamical models. Moreover, the successful candidate will also use and develop new tools related to the coupling of Action FRET with ion mobility (IMS) and/or small angle X-ray or neutron scattering (SAXS/SANS). As a model, we will use the VHS-UIM-SH3 multidomain protein that has been shown to interact with polyubiquitin chains as well as a deubiquitinating enzyme, the three partners containing highly flexible disordered linkers.

The project will be hosted by the analytical science institute located in Lyon/Villeurbanne (France). This new institute comprise around 200 researchers and is among the largest analytical science center in Europe. Cutting edge instruments are available like High field NMR spectrometers (From 600 to 1000MHz). The thesis project will be developed inside the Biosys group and will mainly make use of NMR and will benefit from the expertise of the group members. SAXS and SANS experiments will be conducted et ESRF and ILL facilities while computation will be done by means of GPU equipped computer to allow faster simulations. The successful candidate should have completed (or in stage of completion) M.Sc. degree either in bioinformatics, physical chemistry or related fields. Willingness to learn NMR will be strongly appreciated.