INSTITUT DES SCIENCES ANALYTIQUES

Development of new models for the study of dynamics and interaction of multidomain proteins from NMR and Molecular Dynamics simulations

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Nouveaux modèles pour l'étude de la dynamique et des interactions des protéines multi-domaines par RMN et simulations de dynamique moléculaire

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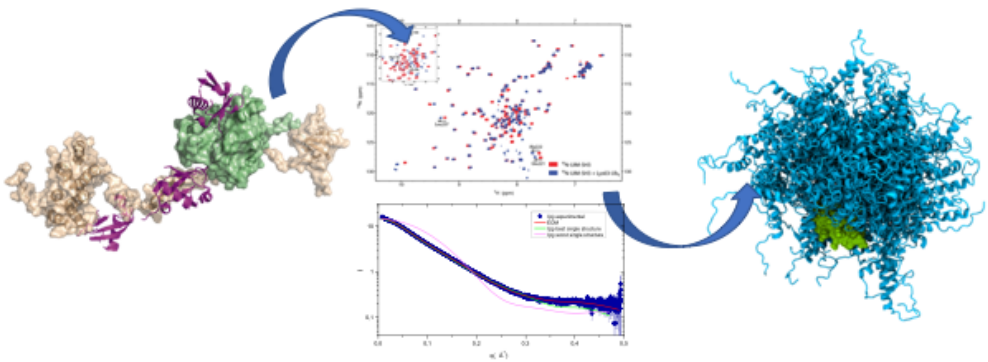
For decades, the classical structure-function paradigm of structural biology has enabled fundamental advances in our understanding of how proteins perform their function and interact with a range of partners. Yet, pioneering studies on intrinsically disordered proteins (IDP) or protein segments (IDS) have revealed that neither the organization in structured folds nor the establishment of stable interactions are strictly necessary for functional interactions involving IDPs or IDSs. These highly heterogeneous interactions range from stable complexes resulting from disorder to order transitions ("folding-upon-binding"), to fuzzy interactions involving complex conformational ensembles. Furthermore, multidomain proteins can simultaneously exhibit well folded domains and highly flexible linkers. In such cases, these linkers enable interface remodeling in response to a variety of partners, modulating the nature, avidity and affinity of interactions in yet-unclear ways. 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 mediators or modulators of macromolecular 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/IDSs in the cell requires novel approaches to describe the dynamics of these challengingly flexible systems and their interactions with an atomic level of details.



This thesis project aims at 1) developing new interpretative models to characterize the dynamics of highly flexible biomolecular systems from NMR experiments, and 2) harness the newly developed approaches in combination with complementary techniques (e.g., SAXS, SANS) to understand the role of IDS in their functional interaction with several partners. In aim 1), the candidate will explore how to synergize Molecular Dynamics simulations with modern machine learning approaches (e.g., self-supervised deep neural networks) to develop computational models for the interpretation of NMR relaxation data that address the limitations of the classical *Model-Free*

framework by accounting for complex conformational dynamics. In aim 2), the candidate will apply the novel developments to describe with atomic-resolution how the dynamics of the VHS-UIM-SH3 multidomain protein modulates its functional interaction with polyubiquitin chains and a deubiquitinating enzyme. Measurements from complementary biophysical methods like SAXS and/or SANS will be integrated to refine the structural and dynamical models. Because of its organization as 3 domains connected by highly flexible disordered segments and its biomedical relevance, VHS-IUM-SH3 is an ideal model system.

The work will be hosted by the Institute of Analytical Sciences (ISA) located in Lyon/Villeurbanne (France). ISA comprises around 200 researchers, recent facilities, and is among the largest analytical science centers in Europe. Cutting edge instruments are available like High field NMR spectrometers (From 600 to 1000MHz). ISA also has a very active and welcoming PhD students'association, ISATOPE. The thesis project will be developed within the Biophysics of Complex Systems (Biosys) research group. Biosys is a dynamic, multidisciplinary group gathering specialists from complementary fields towards the common goal of understanding the structural dynamics of biomedically important proteins. The thesis project will benefit from the multidisciplinary expertise of group members in protein NMR, Molecular Dynamics simulations, and machine learning. We have in-house GPU servers for MD and machine learning, along with access to French national supercomputing resources. SAXS and SANS experiments will be conducted at ESRF. We are seeking a motivated candidate with scientific curiosity, programming skills, and the desire to pursue interdisciplinary research. The successful candidate should have completed (or be in stage of completion) an M.Sc. degree in bioinformatics, physical chemistry or related fields. Familiarity with MD simulations, machine learning, and/or NMR would be strongly appreciated. We note that the candidate will be tasked with computational developments and analyses (programming, modelling) and will not be primarily in charge of experimental data collection (unless they express an interest for it).