Développements de méthodes informatiques pour l'étude dynamique de protéines comportant des segments intrinsèquement destructurés.

Methodological and computational development aiming at the dynamical characterization of intrinsically disordered protein segments.

Supervisors: Dr. Olivier WALKER/ phone: +33.4.37.42.35.45
e-mail: olivier.walker@univ-lyon1.fr

web-site: http://nmrbiolchem.univ-lyon1.fr/

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 phenomenons 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 expanding our previously published approach to predict NMR relaxation parameters or other biophysical methods in the case of multidomain or intrinsically disordered proteins. The successful candidate will have in charge the development of new algorithm based on AI, molecular dynamics and statistical physics.

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 multi-GPU computers to accelerate the diverse calculations. The successful candidate should have completed (or in stage of completion) M.Sc. degree either in physics, mathematics biophysics or related fields. Willingness to learn NMR will be strongly appreciated.

References:

1. Accurate Prediction of Protein NMR Spin Relaxation by Means of Polarizable Force Fields. Application to Strongly Anisotropic Rotational Diffusion

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J. Phys. Chem. B, 2020, 124, 25, 5103–5112
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P-C. Chen, M. Hologne, O. Walker and J. Hennig
J. Chem. Theory. Comput., 2018, 14(2), 1009-1019

3. Computing the Rotational Diffusion of Biomolecules via Molecular Dynamics Simulation and Quaternion Orientations
P.C. Chen, M. Hologne, O. Walker
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