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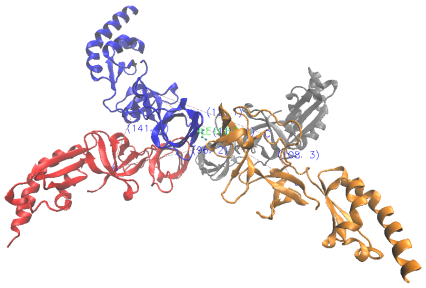

Crystal structure of the homotetramer of amino terminal fragment of FMRP (4ova.pdb)

MASTER INTERNSHIP PROPOSAL

UNVEILING THE STRUCTURE OF FMRP DIMERS, WITH APPLICATIONS TO THE X FRAGILE SYNDROME

Context. Understanding our focus requires two main ingredients. The first one is the *X fragile syndrome*, a genetic disorder often linked to intellectual disability. In all cases, the function of the FMRP protein (Fragile X Mental Retardation Protein) is altered. This is detrimental since FMRP is involved in the transport of mRNA along dendrites within so-called transport granules, thus contributing to the expression of proteins shaping synapsis. The second one is sumoylation, namely the process by which SUMO proteins are (reversibly) attached to target proteins, so as to modify their function. It has been shown that sumoylation contributes to the dissociation of FMRP from transport granules, regulating the transport of mRNA, but the molecular basis of this phenomenon is unkown.

Goals. The amino terminal structure of the FMRP protein was recently solved [1, 2], and of particular interest is the structure 4ova.pdb [2], whose asymmetric unit involves four chains. Three possible dimers were identified from this structure [2]. On the other hand, in order to understand the structure of FMRP in solution, SAXS measurements were obtained.

Unfortunately, these two experimental data are not coherent: simulated SAXS curves from dimers (extracted from the crystal structure, or obtained by sampling conformational ensembles from the latter) do not match the experimental SAXS curves. Consequently, the structure of FMRP in solution remains an open question.

The goal of this internship will be to answer it. In a first step, enhanced models for FMRP dimers will be developed, so as in particular to match experimental SAXS curves. Ideally, this study will unveil the structure of FMRP in solution. In a second step, the structure of FMRP will be used to investigate the molecular basis of sumoylation, in cunjunction with the aforementioned mechanisms.

The methods used will advanced sampling algorithms recently developed and under development in our group [3, 4, 5], available within the Structural Bioinformatics Library ([6], `http://sbl.inria.fr`).

Background. Biophysics, structural bioinformatics.

Misc. The duration is of six months. Possibility to follow-up with a PhD thesis.

References

[1] Leila K Myrick, Hideharu Hashimoto, Xiaodong Cheng, and Stephen T Warren. Human fmrp contains an integral tandem agenet (tudor) and KH motif in the amino terminal domain. *Human molecular genetics*, 24(6):1733–1740, 2015.

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[3] F. Cazals, T. Dreyfus, D. Mazauric, A. Roth, and C.H. Robert. Conformational ensembles and sampled energy landscapes: Analysis and comparison. *J. Comp. Chem.*, 36(16):1213–1231, 2015.

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[5] J. Carr, D. Mazauric, F. Cazals, and D. J. Wales. Energy landscapes and persistent minima. *The Journal of Chemical Physics*, 144(5):4, 2016.

[6] F. Cazals and T. Dreyfus. The Structural Bioinformatics Library: modeling in biomolecular science and beyond. *Bioinformatics*, 7(33):1–8, 2017.