

INTERNSHIP PROPOSAL

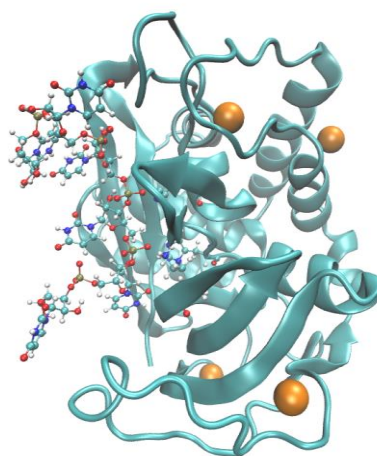
(One page maximum)

Laboratory name: Laboratoire de Biochimie Théorique
CNRS identification code: UPR9080
Internship director's surname: Duboué-Dijon Elise
e-mail: elise.duboue-dijon@cnrs.fr Phone number:
Web page: <http://www-lbt.ibpc.fr/people/duboue-dijon>
Internship location: LBT, IBPC, 13 rue Pierre et Marie Curie, 75005 Paris

Thesis possibility after internship: YES
Funding: NO If YES, which type of funding:

Computational investigation of the molecular mechanism of Ca²⁺-dependent allosteric activation of the EndoU ribonuclease

EndoU is a poorly understood ribonuclease (RNA-cleaving enzyme) found both in bacteria and eukaryotes, including humans. It is a recognized biomarker in several cancers and a potential therapeutic target. Interestingly, its activity is regulated, in eukaryotes, by Ca²⁺ ions, while the bacterial variant does not require any cofactor. Recently, S.Campagne's experimental team in Bordeaux used a combination of several biochemical experiments to suggest a molecular mechanism for this Ca²⁺ triggered activation [1]. They evidenced a change in EndoU conformation upon Ca²⁺ binding and identified several binding sites for Ca²⁺, whose importance was confirmed by mutation experiments. These experiments thus suggest a Ca²⁺-dependent allosteric activation of EndoU, whose molecular details remain to be fully understood. The experiments provide structural insights into the apo and RNA-bound states of EndoU, as well as on the conformational rearrangements occurring upon Ca²⁺ binding but the molecular mechanism allowing for signal communication between the catalytic site and distant Ca²⁺ binding sites remains to be fully characterized.



Using molecular dynamics simulations of both the Ca²⁺-bound and apo EndoU enzyme, isolated or in complex with an RNA substrate, we aim to uncover the molecular details of this Ca²⁺-activated allosteric behavior. Specific strategies to characterize the Ca²⁺-induced rearrangement pathways will be implemented and combined with state-of-the-art force fields for ions. Given the high flexibility of the EndoU-RNA complex, enhanced sampling techniques will also be used to properly characterize the conformational ensemble of the complex in different conditions.

The research will take place in the lab of Theoretical Biochemistry (LBT) with Élise Duboué-Dijon, and will be performed in close collaboration with Sébastien Campagne's experimental team (IECB, U.Bordeaux), where they will be able to perform experiments to test computational findings. Our team is specialized in the simulation, at different scales, of biologically relevant processes, with a focus on RNA and ions.

Methods: Molecular dynamics; Enhanced sampling ; programming for simulation analysis (Python).

Condensed Matter Physics: NO Soft Matter and Biological Physics: YES
Quantum Physics: NO Theoretical Physics: NO