M2 internship

(start Feb. 2025)

CNRS, Laboratoire de Biochimie Théorique, Paris, France

Computational investigation of the molecular mechanism of Ca^{2+}-dependent allosteric activation of the EndoU ribonuclease

Topic

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 Ca^{2+} triggered activation [1]. They evidenced a change in EndoU conformation upon Ca^{2+} binding and identified several binding sites for Ca^{2+}, whose importance was confirmed by mutation experiments. These experiments thus suggest a Ca^{2+}-dependent allosteric activation of EndoU, whose moleculecular details remain to be fully understood. The experiments provide structural insights into the apo (without RNA substrate) and RNA-bound states of EndoU, as well as on the conformational rearrangements occuring upon Ca^{2+} binding but the molecular mechanism allowing for signal communication between the catalytic site and distant Ca^{2+} binding sites remains to be fully characterized.

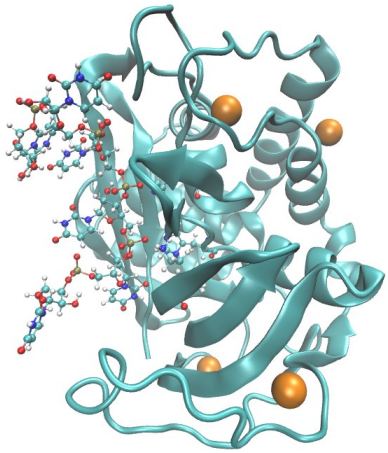

Figure 1: Suggested structure of the EndoU:RNA complex with 4 calcium ions.

Using molecular dynamics simulations of both the Ca^{2+}-bound and apo EndoU enzyme, isolated or in complex with an RNA substrate, we aim to uncover the molecular details of this Ca^{2+}-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.

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

Research environment 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. It is located in the very stimulating research environment of the Latin Quarter, at the heart of Paris.

Contact information Interested candidates should contact Élise Duboué-Dijon (elise.duboue-dijon@cnrs.fr), together with a curriculum vitae and contact information for one or two references.