Master's Thesis Chemistry • From Jan/Feb 2020

CNRS Institut de Biologie Physico-Chimique, Paris, France

Exploring the impact of divalent cations on ribozyme conformational fluctuations with molecular dynamics simulations

Subject RNA sequences that exhibit a catalytic activity similar to that of enzymes, called ribozymes, are found to be involved in an increasing number of biological processes. Hence, understanding the origin of their catalytic activity is a major biochemical challenge to be able to control, modify or tune their activity. [1] An intriguing question is to understand the role played by divalent cations in the ribozyme activity, their activity being related in vivo to the presence of Mg^{2+} ions. [2] The internship will be part of a project that aims to characterize, using molecular simulations, the molecular origin of divalent cations' specificity in the *RzB* Hammerhead ribozyme catalysis. [3,4]

First, we need to determine how different cations (Mg^{2+}, Ca^{2+}, Na^{+}) modulate the ribozyme conformational landscape, which will require the use of advanced sampling techniques. Since traditional non polarizable force fields do not correctly capture the interaction between (divalent) ions and RNA, different descriptions (standard non polarizable, scaled charge, or explicitly polarizable force fields) will need to be compared on small systems where experimental data are available.

The student will determine the most appropriate method to capture ion-phosphate interactions, which are key for RNA or DNA simulations in realistic biological environments. He or she will identify the binding sites and binding modes of different cations in the *RzB* Hammerhead ribozyme, and characterize their impact on the ribozyme conformation fluctuations.

[1] « Ribozymes », W. Scott, *Curr. Op. Struct. Biol.*, **2007**, 17, 280-286

[2] « Metal ions in ribozyme folding and catalysis », R. Hanna, J.A. Doudna, *Curr. Op. Chem. Biol.*,**2000**, 4, 166-170

[3] « Extraordinary rates of transition metal ion-mediated ribozyme catalysis. » M. Roychowdhury-Saha, D.H. Burke, *RNA*, **2006**, 12, 1846-1852

[4] « Two active site divalent ions in the crystal structure of the Hammerhead ribozyme bound to a transition state analogue », A. Mir, B.L. Golden, *Biochemistry*, **2016**, 55, 633-636

Techniques/Methods Molecular dynamics; Standard and polarizable force fields; Enhanced sampling techniques; programming for simulation analysis.

Research environment Research will take place in the lab of Theoretical Biochemistry of the CNRS Institute of Physical and Chemical Biology with Élise Duboué-Dijon. This laboratory is specialized in the simulation, at different scales, of biologically relevant processes. 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-Dijoon **as soon as possible** (duboue-dijon@ibpc.fr), together with a curriculum vitae and contact information for one or two references.