M2 internship — Computational Chemistry

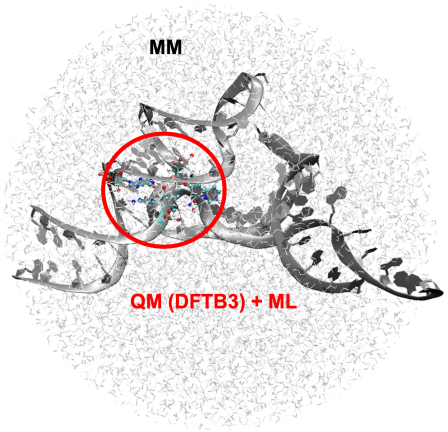
(start Feb. 2023)

CNRS, Laboratoire de Biochimie Théorique, Paris, France

Machine-Learned corrections for highly accurate QM/MM-MD exploration of an ion-dependent ribozyme reaction mechanism

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] The internship will be part of a funded project (ANR MUSIRICAT) that aims to characterize, using molecular simulations, the molecular origin of divalent cations' specificity in the *RzB* Hammerhead ribozyme catalysis. [2] A PhD fellowship starting in Oct. 2023 on the same project will be available.

Specifically, this internship will focus on studying the impact of divalent cations on the reaction mechanism, using a dynamic exploration of the reaction path (Adaptive String Method [3]). Due to their high computational cost, such dynamic QM/MM-MD strategies are usually limited to either low levels of theory (DFTB3) to describe the active site or very short (ps) simulation times. Here, we will develop a workflow to train Machine-Learned (ML) corrections between a low (DFTB3) and high (hybrid DFT) level of theory to describe the reaction. We will use an innovative embedding scheme, developed by our collaborator K. Zinovjev, that will enabling a full QM+ML/MM-MD scheme. These state-of-the-art developments will allow us to achieve high-level description of the active site reactivity, for an only modest additional cost, thus making it possible to reach timescales relevant for local conformational changes and ion rearrangements.



The student will first determine on a small model system of the active site the best strategy to generate (using enhanced sampling techniques) the required diverse set of training points, and to learn robust corrections to the low-level QM part. He or she will then test the ML/MM embedding scheme developed by our collaborator on this small system, before applying it to the full ribozyme system.

[1] W. Scott, *Curr. Op. Struct. Biol.*, **2007**, 17, 280-286
[2] M. Roychowdhury-Saha, D.H. Burke, *RNA*, **2006**, 12, 1846-1852
[3] K. Zinovjev, I. Tunon, *J. Phys. Chem. A*, **2017**, 121, 9764-9772

Techniques/Methods Molecular dynamics; QM/MM ; 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 I. Tunon, K. Zinovjev (U. Valencia, Spain) and G. Stirnemann (LBT, Paris). 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-Dijon (duboue-dijon@ibpc.fr), together with a curriculum vitae and contact information for one or two references.