Multiscale Simulations to Unveil the Role of Divalent Cations in Ribozyme Catalysis

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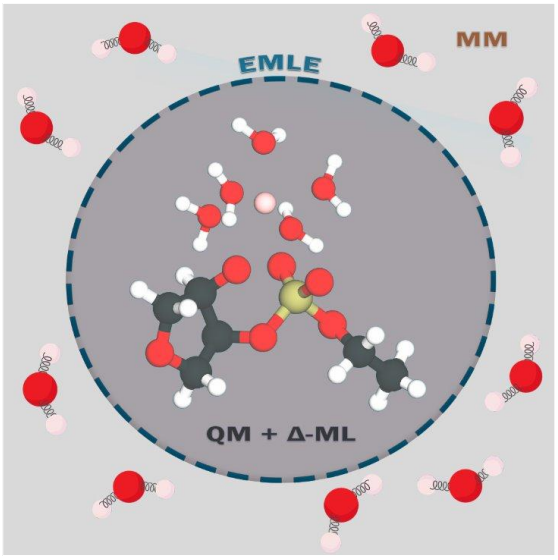
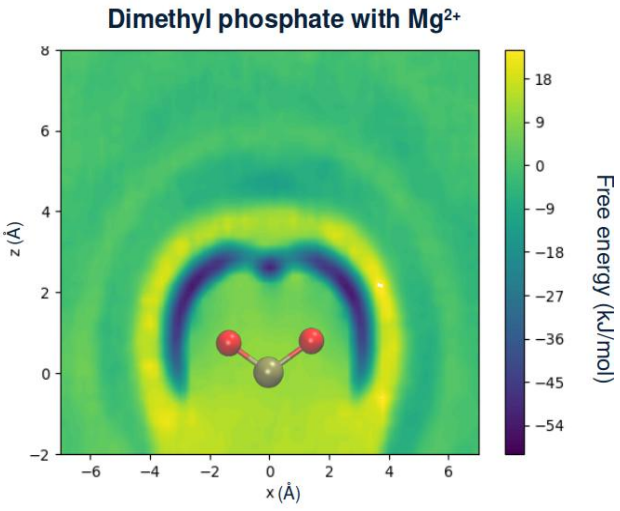
Experiments have shown that the Hammerhead ribozyme catalytic activity vary greatly depending on the nature of the ion in solution: it is 10000 times faster with magnesium ions than sodium ions and 500 times faster than with calcium ions.[1] We aim to provide a molecular explanation for this phenomenon combining advanced conformational exploration with a dynamic exploration of the multiple reaction pathways with the QM/MM-MD Adaptive String Method (ASM).[2] However, we are limited to using semi-empirical functionals for the QM description of such large systems, which affects the accuracy of our simulations. To address this issue and improve accuracy while retaining sampling quality, we propose a QM+ΔML/MM approach, incorporating Machine Learning corrections to achieve DFT-level accuracy without increasing computational cost. We plan to use a newly developed physics-based electrostatic embedding scheme (EMLE) that allows us to apply a ML model trained solely on the QM subsystem *in vacuo*, thus reducing the cost of training the model and allowing for more flexibility of the model.[3] Here we are showing the preliminary result we got so far on a model system focused on the phosphodiester bond only and starting from a deprotonated state to simplify the implementation of the protocol.

Another challenge in such systems is to ensure proper sampling of the different ion binding modes, that are separated by high kinetic barriers.[4] We thus investigate different enhanced sampling strategies to alleviate this issue.





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