ML/MM-MD Simulations to Unveil the Role of Divalent Cations in Ribozyme Catalysis

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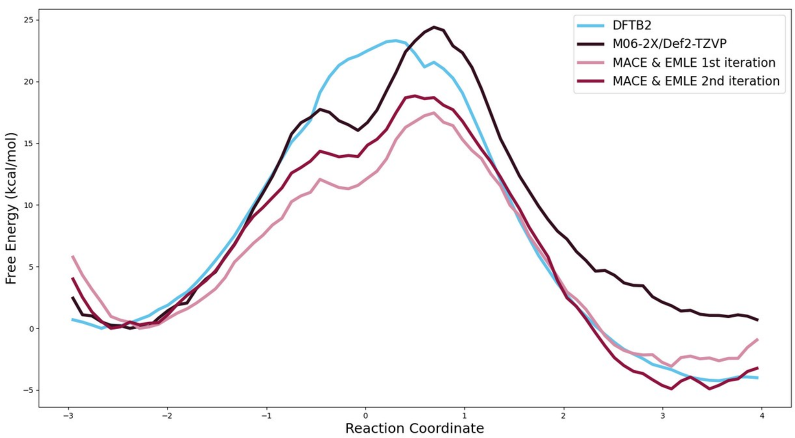
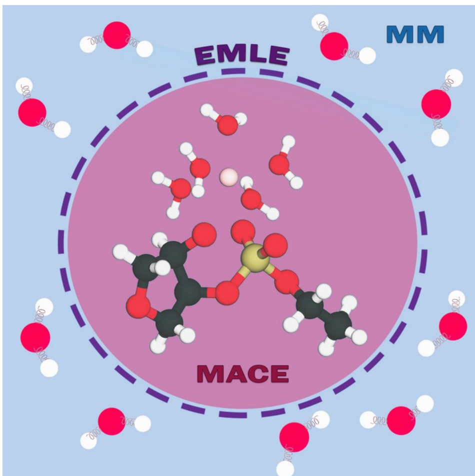
Experiments have shown that the Hammerhead ribozyme catalytic activity vary greatly depending on the nature of the ion in solution: it is 10,000 times faster with magnesium ions than sodium ions and 500 times faster than with calcium ions.[1] We aim to provide a molecular explanation for this phenomenon combining advanced conformational exploration with a dynamic exploration of the multiple reaction pathways using QM/MM-MD and the 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 ML/MM-MD approach, incorporating Machine Learning Potential using MACE[3] to achieve DFT-level accuracy in the catalytic site without increasing computational cost. We test and use a recently suggested physics-based electrostatic embedding scheme, EMLE[4], design for use in ML/MM simulations where the QM electronic density is not available. This scheme allows us to use a ML model trained solely on the QM subsystem *in vacuo*, thus reducing the cost of training the model and allowing for more flexibility.

Here, we demonstrate the promising potential of this approach on a model system focused on the phosphodiester bond cleavage.





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