

# New efficient electrostatic embedding QM/MM model in periodic boundary conditions

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## ABSTRACT

Long-range electrostatics interactions have been proven fundamental for correctly describing chemical reactivity in the condensed phase. Protein simulation in Periodic Boundary Conditions (PBC) via Ewald summation has become a standard in Molecular Mechanics simulations, but are scarce in *ab initio* Quantum Mechanical / Molecular Mechanics (QM/MM) models. We have recently proposed a new electrostatic embedding PBC-adapted QM/MM model based on electrostatic potential fitted (ESPF) charges that is efficient, simple to implement, and compatible with Density Functional Theory (DFT).[1-2] The proposed model exploits the advantages of ESPF charge operators to reproduce the quantum density in replicas,[3] and takes advantage of the  $O(N \cdot \log N)$  scaling of the Smooth Particle Mesh Ewald for the description of the long-range electrostatic interactions.[4] The availability of the total energy and its analytical first derivatives allows running Molecular Dynamics (MD) in the most common thermodynamical ensembles. We simulated the free energy profile for the trans-to-cis isomerization of proline in water, showing a qualitatively correct reaction barrier. Additionally, the performances of a different variety of DFT functionals for simulating isomerization reaction profiles are reported.

## References

- [1] Bonfrate, S.; Ferré, N. and Huix-Rotllant, M. An efficient electrostatic embedding QM/MM method using periodic boundary conditions based on particle-mesh Ewald sums and electrostatic potential fitted charge operators. *J. Chem. Phys.*, **2023**, *158*, 021101.
- [2] Bonfrate, S.; Ferré, N. and Huix-Rotllant, M. Analytic gradients for the electrostatic embedding QM/MM in periodic boundary conditions using particle-mesh Ewald sums and electrostatic potential fitted charge operators. *ChemRxiv*. **2024**; (available at [doi:10.26434/chemrxiv-2024-5tzsf](https://doi.org/10.26434/chemrxiv-2024-5tzsf)).
- [3] Ferré, N. and Ángyán, J. G. Approximate electrostatic interaction operator for QM/MM calculations. *Chem. Phys. Lett.*, **2002**, *356*, 331.
- [4] Essmann, U.; Perera, L.; Berkowitz, M. L.; Darden, T.; Lee, H. and Pedersen, L. G. A Smooth Particle Mesh Ewald Method. *J. Chem. Phys.*, **1995**, *103*, 8577.