An Efficient Particle Mesh Ewald Approach for Including Long-Range Electrostatics in QM/MM Molecular Dynamics Simulations

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Abstract

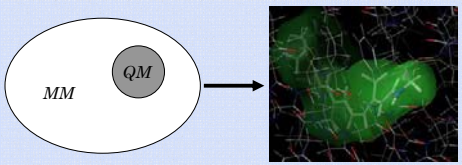
The importance of including long range electrostatics in classical molecular dynamics simulations has been understood for many years. However, similar issues with combined QM/MM MD simulations have tended to be neglected because of the incompatibility of the traditional Ewald and Particle Mesh Ewald methods with QM calculations. Recently a number of researchers have published details of traditional Ewald approaches that are compatible with QM/MM calculations[1,2]. The computational expense of such approaches, which scale as O(N^2), however, makes their use in QM/MM MD simulations of enzymes in explicit solvent inappropriate. We present here a modification of the FFT based Particle Mesh Ewald (PME) approach, implemented in AMBER v9.0, that is suitable for QM/MM MD calculations. The O(Nln[N]) scaling of the PME approach makes it significantly more efficient for even relatively small proteins in explicit solvent.

QM/MM Background

The QM/MM approach to molecular dynamics combines a quantum mechanical (QM) potential with a more *approximate* molecular mechanical (MM) potential.

$$E_{system} = E_{MM} + E_{QM} + E_{QM/MM}$$

We have implemented this in the latest version of the AMBER software (v9.0)[3] so that the part of the system that is of chemical interest (*e.g.* the active site) can be treated with a semi-empirical quantum part and the rest with the classical AMBER force field.



QM/MM has some big advantages for MD simulations:

- MM calculations do not allow for bond breaking or formation. Therefore without a QM potential reactions cannot be directly simulated.
- Pure QM calculations are very computationally costly. QM/MM provides an acceptable tradeoff between the accuracy of a QM potential and the speed of an MM potential.

References

1) Nam, K.; Gao, J. L.; York, D. *Journal of Chemical Theory and Computation* **2005**, *1*, 2.

2) Laino, T.; Mohamed, F.; Laio, A.; Parrinello, M. *Journal Of Chemical Theory And Computation* **2006**, *2*, 1370.

3) Walker, R.C.; Crowley, M.F.; Case, D.A., *Journal of Computational Chemistry*, **2007**, in prep.

4) Ewald, P. P. *Annalen Der Physik* **1921**, *64*, 253.

5) Darden, T.; York, D.; Pedersen, L. *Journal of Chemical Physics* **1993**, *98*, 10089.

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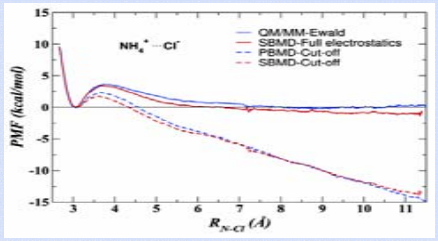
Long Range Electrostatics

It is well known that electrostatic interactions are long ranged and simple truncation at a cut-off distance causes simulation artefacts.



Comparison of potential of mean force (PMF) profiles for the ionic separation ($R_{N\text{-}Cl}$) of ammonium chloride ($NH_4^+\cdots Cl^-$) in water. Dashed lines represent cut-off (11.5 Å) approaches. (Adapted from Nam *et al*[1]).

In classical MM simulations the infinite electrostatic contributions are included by dividing the infinite sum between direct and reciprocal contributions. Evaluation is achieved through the use of an Ewald[4] or Particle Mesh Ewald[5] approach.

QM/MM Compatible PME

In QM/MM calculations, however, the problem is complicated by the fact that the QM atoms are not evaluated as point charges. Similarly the charge density of the QM atoms is a function of the infinite field of charges including the images of the QM atoms.

Recently Nam *et al.* published an Ewald compatible QM/MM approach[1]. This method provides a correct implementation of long-range electrostatics in periodic systems, but it is very slow for any sizeable simulation system. Here we describe how a faster PME alternative can be adapted for QM/MM.

We can write the periodic energy as:

$$E^{Periodic} = E^{Periodic}[\rho,\rho] + E^{Periodic}[\rho,q] + E^{Periodic}[q,q]$$

where q are the static partial charges of the MM atoms and ρ represents the electron density and core charges of the QM region and the $[\rho,q]$ notation implies the interaction of ρ with q. We can rewrite this as

$$E^{Periodic} = E^{RS} + \Delta E^{PBC}$$

where E^{RS} is the conventional cutoff energy and ΔE^{PBC} is a periodic boundary correction term. The key approximation we make is that the full charge density in $\Delta E^{PBC}[\rho,\rho]$ and $\Delta E^{PBC}[\rho,q]$ can be replaced by Mulliken charges, denoted Q:

$$\Delta E^{PBC}[\rho,\rho] = E^{Periodic}[\rho,\rho] - E^{RS}[\rho,\rho]$$
$$\approx E^{Periodic}[Q,Q] - E^{RS}[Q,Q] = \Delta E^{PBC}[Q,Q]$$

Expanding E$^{\text{periodic}}$ as an Ewald sum gives:

$$\Delta E^{PBC}[Q,Q] = E^{recip}[Q,Q] + E^{direct}[Q,Q] - E^{RS}[Q,Q]$$
$$= E^{recip}[Q,Q] + \frac{1}{2}\sum_i^{QM}\sum_{j\neq i}^{QM} Q_i Q_j \frac{erfc(\kappa r_{ij})}{r_{ij}} + \sum_i^{QM} Q_i^2 \frac{\kappa}{\sqrt{\pi}} - \frac{1}{2}\sum_i^{QM}\sum_{j\neq i}^{QM} Q_i Q_j \frac{1}{r_{ij}}$$
$$= E^{recip}[Q,Q] + \sum_i^{QM} Q_i^2 \frac{\kappa}{\sqrt{\pi}} - \frac{1}{2}\sum_i^{QM}\sum_{j\neq i}^{QM} Q_i Q_j \frac{erf(\kappa r_{ij})}{r_{ij}}$$
$$= E^{recip}[Q,Q] + \Delta E^{PBC}_{cutoff}[Q,Q]$$

QM/MM Compatible PME Contd.

The equivalent treatment is also used for $\Delta E^{PBC}[Q,q]$; since an atom cannot be both a QM and MM atom this simplifies to:

$$\Delta E^{PBC}[Q,q] = E^{recip}[Q,q] + \sum_i^{QM} Q_i \sum_j^{MM} q_j \frac{erf(\kappa r_{ij})}{r_{ij}}$$

Introducing the ΔE^{PBC} Mulliken charge approximation allows us to write the periodic energy as:

$$E^{Periodic} \approx E^{RS}[\rho,\rho] + \Delta E^{PBC}[Q,Q]$$
$$+ E^{RS}[\rho,q] + \Delta E^{PBC}[Q,q]$$
$$+ E^{recip}[q,q] + E^{direct}[q,q]$$

The E^{RS} terms are treated using the regular cutoff approximation. The second term of the equation above is treated with a regular Ewald method while the fourth and fifth terms, are the same as Nam *et al.* except that the reciprocal-space K-sum is replaced with a PME method. In particular the fourth term has the form:

$$\Delta E^{PBC}[Q,q] = E^{Periodic}[Q,q] - E^{RS}[Q,q]$$
$$= \sum_i^{QM} Q_i \sum_j^{MM} q_j \left(\Psi^{Periodic}_{Ewald}(\vec{R}_i,\vec{R}_j) - \Psi^{RS}(R_{i,j})\right)$$
$$= \sum_i^{QM} Q_i \sum_j^{MM} q_j \left(\Delta\Psi^{PBC}(R_{i,j})\right)$$

where $\Psi^{Periodic}_{Ewald}$ is the Ewald pair potential and Ψ^{RS} the coulomb potential within a cutoff. The combination of these potentials yields the following correction potential:

$$\Delta\Psi^{PBC}(R_{i,j}) = \Psi^{recip}(\vec{R}_i,\vec{R}_j) + \Psi^{direct}(R_{i,j}) - \Psi^{RS}(R_{i,j})$$
$$= \Psi^{recip}(\vec{R}_i,\vec{R}_j) + \Delta\Psi^{PBC}_{cutoff}(R_{i,j})$$

where $\Psi^{recip}(\vec{R}_i,\vec{R}_j)$ is the reciprocal part of the Ewald pair potential due to all MM atoms interacting with QM atoms represented as Mulliken charges, and $\Delta\Psi^{PBC}_{cutoff}(R_{i,j})$ is the correction to the cutoff based real-space potential as calculated in the normal QM/MM non-periodic method. The reciprocal part in the above equation can be conveniently written as an Ewald sum but this is slow for large numbers of MM atoms. Writing the Ewald sum in terms of the total reciprocal sum energy of all atoms calculated with PME and all atoms represented by point charges (where q* implies all charges), we can isolate the term in question:

$$E^{recip}_{PME}(q^*) = \frac{1}{2}\sum_{i=1}^{allatoms}\sum_{j=1}^{allatoms} q_i^* q_j^* \left(\Psi^{recip}_{PME}(\vec{R},\vec{R})\right)$$
$$= \frac{1}{2}\sum_{i=1}^{QM}\sum_{j=1}^{QM} Q_i Q_j \left(\Psi^{recip}_{PME}(\vec{R},\vec{R})\right) + \sum_{i=1}^{QM}\sum_{j=1}^{MM} Q_i q_j \left(\Psi^{recip}_{PME}(\vec{R},\vec{R})\right) + \frac{1}{2}\sum_{i=1}^{MM}\sum_{j=1}^{MM} q_i q_j \left(\Psi^{recip}_{PME}(\vec{R},\vec{R})\right)$$

and rearranging for the terms we need,

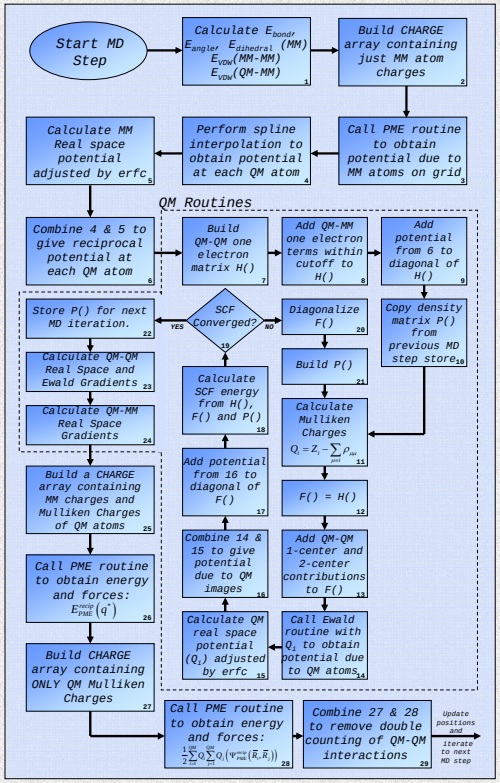
$$\sum_{i=1}^{QM}\sum_{j=1}^{MM} Q_i q_j \left(\Psi^{recip}_{PME}(\vec{R},\vec{R})\right) + \frac{1}{2}\sum_{i=1}^{MM}\sum_{j=1}^{MM} q_i q_j \left(\Psi^{recip}_{PME}(\vec{R},\vec{R})\right) = E^{recip}_{PME}(q^*) - \frac{1}{2}\sum_{i=1}^{QM}\sum_{j=1}^{QM} Q_i Q_j \left(\Psi^{recip}_{PME}(\vec{R},\vec{R})\right)$$

Thus the energies and forces from the reciprocal sum on the left of the above equation can be determined from the difference of the results of a PME reciprocal sum of all the charges and a PME reciprocal sumo of just the Mulliken charges. Thus we can re-write our definition of E$^{\text{Periodic}}$ above as:

$$E^{Periodic} \approx E^{RS}[\rho,\rho] + E^{recip}_{Ewald}[Q,Q] + \Delta E^{PBC}_{cutoff}[Q,Q] + E^{RS}[\rho,q]$$
$$+ \Delta E^{PBC}_{cutoff}[Q,q] + \left(E^{recip}_{PME}[q^*] - E^{recip}_{PME}[Q,Q]\right) + E^{direct}_{PME}[q,q]$$

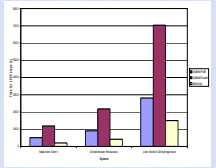
Terms 1 to 4 come from the QM calculation which includes a regular Ewald treatment of the periodic images of the QM atoms and a cut-off treatment of the electrostatic field from the static MM partial charges. Terms 5 and 6 are calculated by two PME calculations described above after the Mulliken charges have been determined and the final term is the classical direct space calculation over static MM charges.

Calculation Flowchart



Performance Comparison

The table and plot below show a comparison for the time required to complete 1,000 MD steps on 1 cpu of a Pentium-D 3.2GHz System for QM/MM with either a PME or an Ewald treatment of the QM/MM long range electrostatic interactions. QM/QM interactions always use an Ewald approach while MM/MM interactions always use a PME approach. Pure classical simulation timings are shown for comparison.



System	NATOM (NQM)	QMMM (PME)	QMMM (Ewald)*	MM Only	Ratio QMMM / MM Only (PME/Ewald)
Malachite Green	12,612 (50 QM)	514 s	1183 s	210 s	2.45 / 5.63
Dihydrofolate Reductase	23,558 (66 QM)*	919 s	2189 s	420 s	2.19 / 5.22
Liver Alcohol Dehydrogenase	76,723 (71 QM)	2818 s	7032 s	1505 s	1.87 / 4.67

* Timings here are for QM-MM and QM-QM interactions calculated using Ewald and MM-MM interactions calculated using PME. An 8 Angstrom cut-off was used for the direct space sum of both the electrostatic and van der Waals interactions.
* Consists of 65 MM atoms treated quantum mechanically and 1 link atom.