Implementation of Periodic Boundary Condition Quantum Mechanical Molecular Mechanical Calculations Using the Q-Chem and NAMD Software Packages

Xiaoliang Pan and Yihan

The total QM/MM interaction for a periodic system is

$$E = \frac{1}{2}\left\langle \rho_{QM} + q_{MM} \middle| \hat{j}_{\mathbf{n}} \middle| \rho_{QM} + q_{MM} \right\rangle$$
$$= E_{QM,QM} + E_{QM,MM} + E_{MM.MM} \quad (1)$$

It three components are

$$E_{QM,QM} = \frac{1}{2}\left\langle \rho_{QM} \middle| \hat{j}_{\mathbf{n}} \middle| \rho_{QM} \right\rangle = \frac{1}{2}\left\langle \rho_{QM} | \phi_{QM,\mathbf{n}} \right\rangle \quad (2)$$
$$E_{QM,MM} = \left\langle \rho_{QM} \middle| \hat{j}_{\mathbf{n}} \middle| q_{MM} \right\rangle = \left\langle \rho_{QM} | \phi_{MM,\mathbf{n}} \right\rangle \quad (3)$$
$$E_{MM,MM} = \frac{1}{2}\left\langle q_{MM} \middle| \hat{j}_{\mathbf{n}} \middle| q_{MM} \right\rangle \quad (4)$$

where the electrostatic potential of the QM (or MM) subsystem and its images are denoted by $\phi_{QM,\mathbf{n}}$ (or $\phi_{MM,\mathbf{n}}$).

Following the notation from Giese and York, let us split the Coulomb operator $\hat{j}_{\mathbf{n}}$ into central-cell and extra contributions:

$$\hat{j}_{\mathbf{n}} = \hat{j} + \hat{j}_{\Delta} \quad (5)$$

There are several approximations one can make to the QM-QM interaction energy:

- Ewald methods ("QM/MM-Ewald") from Nam, Gao and York, and from Holden, Richard and Herbert.

$$E^{Ewald}_{QM,QM} = \frac{1}{2}\left\langle \rho_{QM} \middle| \hat{j} \middle| \rho_{QM} \right\rangle + \frac{1}{2}\left\langle Q_{QM} \middle| \hat{j}_{\Delta} \middle| Q_{QM} \right\rangle$$
$$= \frac{1}{2}\left\langle \rho_{QM} \middle| \hat{j} \middle| \rho_{QM} \right\rangle - \frac{1}{2}\left\langle Q_{QM} \middle| \hat{j} \middle| Q_{QM} \right\rangle + \frac{1}{2}\left\langle Q_{QM} \middle| \hat{j}_{\mathbf{n}} \middle| Q_{QM} \right\rangle \quad (6)$$

  which performs an Ewald sum over Mulliken or ChElPG charges, and then corrects the QM-QM interactions within the central unit cell. This leads to $E^{Ewq-Mulliken}_{QM,QM}$ and $E^{Ewq-ChElPG}_{QM,QM}$ models.

- Particle Mesh Ewald methods ("QM/MM-PME-C"), which employs atomic charges to represent QM images,

$$E^{PME-Q}_{QM,QM} = \frac{1}{2}\left\langle \rho_{QM} \middle| \hat{j} \middle| \rho_{QM} \right\rangle + \alpha \left\langle \rho_{QM} \middle| \hat{j}_{\Delta} \middle| Q_{QM} \right\rangle + (\frac{1}{2} - \alpha)\left\langle Q_{QM} \middle| \hat{j}_{\Delta} \middle| Q_{QM} \right\rangle \quad (7)$$

Here the second term in Eq. 9 can be broken into real-space and reciprocal-space components:

$$\begin{aligned}\left\langle \rho_{QM} \middle| \hat{j}_{\Delta} \middle| Q_{QM} \right\rangle &= \langle \rho_{QM} | \phi_{\Delta}(Q_{QM}) \rangle \\ &= \langle \rho_{QM} | \phi_{\mathbf{n}}(Q_{QM}) - \phi(Q_{QM}) \rangle \\ &= \langle \rho_{QM} | \phi_{\mathbf{n},real}(Q_{QM}) + \phi_{\mathbf{n},recip}(Q_{QM}) - \phi(Q_{QM}) \rangle \\ &= \langle \rho_{QM} | \phi_{\mathbf{n},real}(Q_{QM}) - \phi(Q_{QM}) \rangle + \langle \rho_{QM} | \phi_{\mathbf{n},recip}(Q_{QM}) \rangle \\ &= -\left\langle \rho_{QM} \middle| \hat{j}_{erf} \middle| Q_{QM} \right\rangle + \langle \rho_{QM} | \phi_{\mathbf{n},recip}(Q_{QM}) \rangle \end{aligned} \tag{8}$$

while the third term, $\left\langle Q_{QM} \middle| \hat{j}_{\Delta} \middle| Q_{QM} \right\rangle$, in Eq. 9 can be treated the same way as in QM/MM-Ewald. Note that, as a PME method, the reciprocal component in Eq. 8 requires us to spread the reciprocal potential from QM atomic charges onto an atom-centered grid before it can be integrated together with the electron density. This reciprocal component contributes to the Fock matrix not only through the electron density (on the bra side) but also the QM atomic charges (on the ket side), and it is unclear how to the latter can be computed efficiently within the reciprocal space. One way to completely avoid the ket-side contribution is to fix the QM atomic charges to reference values (i.e. kept constant throughout the simulation),

$$E_{QM,QM}^{QM/MM-FC} = \frac{1}{2} \left\langle \rho_{QM} \middle| \hat{j} \middle| \rho_{QM} \right\rangle + \alpha \left\langle \rho_{QM} \middle| \hat{j}_{\Delta} \middle| Q_{QM}^{ref} \right\rangle + (\frac{1}{2} - \alpha) \left\langle Q_{QM}^{ref} \middle| \hat{j}_{\Delta} \middle| Q_{QM}^{ref} \right\rangle \tag{9}$$

where the second term becomes

$$\left\langle \rho_{QM} \middle| \hat{j}_{\Delta} \middle| Q_{QM}^{ref} \right\rangle = -\left\langle \rho_{QM} \middle| \hat{j}_{erf} \middle| Q_{QM}^{ref} \right\rangle + \left\langle \rho_{QM} \middle| \phi_{\mathbf{n},recip}(Q_{QM}^{ref}) \right\rangle \tag{10}$$

When the α coefficient is set to 1, this leads to the ambient-potential QM/MM method ("cEw") of Giese and York.

- PME method using electron density for QM images ("QM/MM-PME-D"), and the energy will be

$$E_{QM,QM}^{PME-D} = \frac{1}{2} \left\langle \rho_{QM} \middle| \hat{j}_{erfc} \middle| \rho_{QM} \right\rangle + \frac{1}{2} \langle \rho_{QM} | \phi_{\mathbf{n},recip}(\rho_{QM}) \rangle \tag{11}$$

It requires the use of $erfc(\xi r)/r$ operator instead of $1/r$ in the real-space evaluation of Coulomb integrals, as well as a representation for the QM density/potential on both cubic grids (for reciprocal-space calculation) and atomc-centered grids (for integration). While all necessary code components can be readily found from QM software packages, such as Q-Chem and QPS, and from common MM software packages, they have yet to be assembled together.

TABLE I: Different options for handling QM-QM interactions in a QM/MM calculation.

Method	Energy	Expression	Comments
Non-PBC	Total	$\frac{1}{2}\left\langle \rho_{QM} \middle\| \hat{j} \middle\| \rho_{QM} \right\rangle$	
	Real Space	$\frac{1}{2}\left\langle \rho_{QM} \middle\| \hat{j} \middle\| \rho_{QM} \right\rangle$	
	Reciprocal Space	None	
Ewald	Total	$\frac{1}{2}\left\langle \rho_{QM} \middle\| \hat{j} \middle\| \rho_{QM} \right\rangle + \frac{1}{2}\left[\left\langle Q_{QM} \middle\| \hat{j}_{\mathbf{n}} \middle\| Q_{QM} \right\rangle - \left\langle Q_{QM} \middle\| \hat{j} \middle\| Q_{QM} \right\rangle\right]$	"Ewq"
	Real Space	$\frac{1}{2}\left\langle \rho_{QM} \middle\| \hat{j} \middle\| \rho_{QM} \right\rangle - \frac{1}{2}\left\langle Q_{QM} \middle\| \hat{j}_{erf} \middle\| Q_{QM} \right\rangle$	
	Reciprocal Space	$\frac{1}{2}\left\langle Q_{QM} \middle\| \phi_{\mathbf{n},recip}(Q_{QM}) \right\rangle$	
Ewald-FQ	Total	$\frac{1}{2}\left\langle \rho_{QM} \middle\| \hat{j} \middle\| \rho_{QM} \right\rangle + \frac{1}{2}\left[\left\langle Q^{ref}_{QM} \middle\| \hat{j}_{\mathbf{n}} \middle\| Q^{ref}_{QM} \right\rangle - \left\langle Q^{ref}_{QM} \middle\| \hat{j} \middle\| Q^{ref}_{QM} \right\rangle\right]$	"MMEw"
	Real Space	$\frac{1}{2}\left\langle \rho_{QM} \middle\| \hat{j} \middle\| \rho_{QM} \right\rangle - \frac{1}{2}\left\langle Q^{ref}_{QM} \middle\| \hat{j}_{erf} \middle\| Q^{ref}_{QM} \right\rangle$	
	Reciprocal Space	$\frac{1}{2}\left\langle Q^{ref}_{QM} \middle\| \phi_{\mathbf{n},recip}(Q^{ref}_{QM}) \right\rangle$	
PME-Q	Total	$\frac{1}{2}\left\langle \rho_{QM} \middle\| \hat{j} \middle\| \rho_{QM} \right\rangle + \alpha\left[\left\langle \rho_{QM} \middle\| \hat{j}_{\mathbf{n}} \middle\| Q_{QM} \right\rangle - \left\langle \rho_{QM} \middle\| \hat{j} \middle\| Q_{QM} \right\rangle\right]$ $+\left(\frac{1}{2}-\alpha\right)\left[\left\langle Q_{QM} \middle\| \hat{j}_{\mathbf{n}} \middle\| Q_{QM} \right\rangle - \left\langle Q_{QM} \middle\| \hat{j} \middle\| Q_{QM} \right\rangle\right]$	
	RealSpace	$\frac{1}{2}\left\langle \rho_{QM} \middle\| \hat{j} \middle\| \rho_{QM} \right\rangle - \alpha\left\langle \rho_{QM} \middle\| \hat{j}_{erf} \middle\| Q_{QM} \right\rangle - \left(\frac{1}{2}-\alpha\right)\left\langle Q_{QM} \middle\| \hat{j}_{erf} \middle\| Q_{QM} \right\rangle$	
	Reciprocal Space	$\alpha\left\langle \rho_{QM} \middle\| \phi_{\mathbf{n},recip}(Q_{QM}) \right\rangle + \left(\frac{1}{2}-\alpha\right)\left\langle Q_{QM} \middle\| \phi_{\mathbf{n},recip}(Q_{QM}) \right\rangle$	
PME-FQ	Total	$\frac{1}{2}\left\langle \rho_{QM} \middle\| \hat{j} \middle\| \rho_{QM} \right\rangle + \alpha\left[\left\langle \rho_{QM} \middle\| \hat{j}_{\mathbf{n}} \middle\| Q^{ref}_{QM} \right\rangle - \left\langle \rho_{QM} \middle\| \hat{j} \middle\| Q^{ref}_{QM} \right\rangle\right]$ $+\left(\frac{1}{2}-\alpha\right)\left[\left\langle Q^{ref}_{QM} \middle\| \hat{j}_{\mathbf{n}} \middle\| Q^{ref}_{QM} \right\rangle - \left\langle Q^{ref}_{QM} \middle\| \hat{j} \middle\| Q^{ref}_{QM} \right\rangle\right]$	"CEw"
	Real Space	$\frac{1}{2}\left\langle \rho_{QM} \middle\| \hat{j} \middle\| \rho_{QM} \right\rangle - \alpha\left\langle \rho_{QM} \middle\| \hat{j}_{erf} \middle\| Q^{ref}_{QM} \right\rangle - \left(\frac{1}{2}-\alpha\right)\left\langle Q^{ref}_{QM} \middle\| \hat{j}_{erf} \middle\| Q^{ref}_{QM} \right\rangle$	
	Reciprocal Space	$\alpha\left\langle \rho_{QM} \middle\| \phi_{\mathbf{n},recip}(Q^{ref}_{QM}) \right\rangle + \left(\frac{1}{2}-\alpha\right)\left\langle Q^{ref}_{QM} \middle\| \phi_{\mathbf{n},recip}(Q^{ref}_{QM}) \right\rangle$	
PME-D	Total	$\frac{1}{2}\left\langle \rho_{QM} \middle\| \hat{j}_{\mathbf{n}} \middle\| \rho_{QM} \right\rangle$	
	Real Space	$\frac{1}{2}\left\langle \rho_{QM} \middle\| \hat{j}_{erfc} \middle\| \rho_{QM} \right\rangle$	
	Reciprocal Space	$\frac{1}{2}\left\langle \rho_{QM} \middle\| \phi_{\mathbf{n},recip}(\rho_{QM}) \right\rangle$	

TABLE II: Different options for handling QM-MM interactions in a QM/MM calculation.

Method	Energy	Expression	Comments
Cutoff-h	Total	$\left\langle \rho_{QM} \middle\| \hat{j}h(r_C - r) \middle\| q_{MM} \right\rangle$	
	Real Space	$\left\langle \rho_{QM} \middle\| \hat{j}h(r_C - r) \middle\| q_{MM} \right\rangle$	
	Reciprocal Space	None	
Cutoff-s	Total	$\left\langle \rho_{QM} \middle\| \hat{j}s(r - r_C) \middle\| q_{MM} \right\rangle$	
	Real Space	$\left\langle \rho_{QM} \middle\| \hat{j}s(r - r_C) \middle\| q_{MM} \right\rangle$	
	Reciprocal Space	None	
Ewald	Total	$\left\langle \rho_{QM} \middle\| \hat{j}h(r_C - r) \middle\| q_{MM} \right\rangle + \left\langle Q_{QM} \middle\| \hat{j}_{\mathbf{n}} \middle\| q_{MM} \right\rangle$ $- \left\langle Q_{QM} \middle\| \hat{j}h(r_C - r) \middle\| q_{MM} \right\rangle$	"Ewq"
	Real Space	$\left\langle \rho_{QM} \middle\| \hat{j}h(r_C - r) \middle\| q_{MM} \right\rangle - \left\langle Q_{QM} \middle\| \hat{j}_{erf}h(r_C - r) \middle\| q_{MM} \right\rangle$	
	Reciprocal Space	$\langle Q_{QM} \| \phi_{\mathbf{n},recip}(q_{MM}) \rangle$	
Ewald-2	Total	$\left\langle \rho_{QM} \middle\| \hat{j} \middle\| q_{MM} \right\rangle + \left\langle Q_{QM} \middle\| \hat{j}_{\mathbf{n}} \middle\| q_{MM} \right\rangle$ $- \left\langle Q_{QM} \middle\| \hat{j}_{erfc}h(r_C - r) \middle\| q_{MM} \right\rangle - \left\langle \rho_{QM} \middle\| \hat{j}_{erf}h(r_C - r) \middle\| q_{MM} \right\rangle$	
	Real Space	$\left\langle \rho_{QM} \middle\| \hat{j}_{erfc}h(r_C - r) \middle\| q_{MM} \right\rangle$	
	Reciprocal Space	$\langle Q_{QM} \| \phi_{\mathbf{n},recip}(q_{MM}) \rangle$	
Ewald-s	Total	$\left\langle \rho_{QM} \middle\| \hat{j}s(r - r_C) \middle\| q_{MM} \right\rangle + \left\langle Q_{QM} \middle\| \hat{j}_{\mathbf{n}} \middle\| q_{MM} \right\rangle$ $- \left\langle Q_{QM} \middle\| \hat{j}s(r - r_C) \middle\| q_{MM} \right\rangle$	
	Real Space	$\left\langle \rho_{QM} \middle\| \hat{j}s(r - r_C) \middle\| q_{MM} \right\rangle$ $+ \left\langle Q_{QM} \middle\| \left[\hat{j}_{erfc}h(r_C - r) - \hat{j}s(r - r_C) \right] \middle\| q_{MM} \right\rangle$	
	Reciprocal Space	$\langle Q_{QM} \| \phi_{\mathbf{n},recip}(q_{MM}) \rangle$	
Ewald-sFQ	Total	$\left\langle \rho_{QM} \middle\| \hat{j}s(r - r_C) \middle\| q_{MM} \right\rangle + \left\langle Q^{ref}_{QM} \middle\| \hat{j}_{\mathbf{n}} \middle\| q_{MM} \right\rangle$ $- \left\langle Q^{ref}_{QM} \middle\| \hat{j}s(r - r_C) \middle\| q_{MM} \right\rangle$	"MMEw"
	Real Space	$\left\langle \rho_{QM} \middle\| \hat{j}s(r - r_C) \middle\| q_{MM} \right\rangle$ $+ \left\langle Q^{ref}_{QM} \middle\| \left[\hat{j}_{erfc}h(r_C - r) - \hat{j}s(r - r_C) \right] \middle\| q_{MM} \right\rangle$	
	Reciprocal Space	$\left\langle Q^{ref}_{QM} \middle\| \phi_{\mathbf{n},recip}(q_{MM}) \right\rangle$	
PME	Total	$\left\langle \rho_{QM} \middle\| \hat{j}_{\mathbf{n}} \middle\| q_{MM} \right\rangle$	"CEw"
	Real Space	$\left\langle \rho_{QM} \middle\| \hat{j}_{erfc}h(r_C - r) \middle\| q_{MM} \right\rangle$	
	Reciprocal Space	$\langle \rho_{QM} \| \phi_{\mathbf{n},recip}(q_{MM}) \rangle$	