A Hamiltonian electrostatic coupling scheme for hybrid Car–Parrinello molecular dynamics simulations

Alessandro Laio, Joost VandeVondele, and Ursula Rothlisberger
Laboratory of Inorganic Chemistry, ETH Zurich, 8093 Zürich, Switzerland
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We present a fully Hamiltonian and computationally efficient scheme to include the electrostatic effects due to the classical environment in a Car–Parrinello mixed quantum Mechanics/molecular mechanics (QM/MM) method. The polarization due to the MM atoms close to the quantum system is described by a Coulombic potential modified at short range. We show that the functional form of this potential has to be chosen carefully in order to obtain the correct interaction properties and to prevent an unphysical escape of the electronic density to the MM atoms (the so-called spill-out effect). The interaction between the QM system and the more distant MM atoms is modeled by a Hamiltonian term explicitly coupling the multipole moments of the quantum charge distribution with the classical point charges. Our approach remedies some of the well known deficiencies of current electrostatic coupling schemes in QM/MM methods, allowing molecular dynamics simulations of mixed systems within a fully consistent and energy conserving approach. © 2002 American Institute of Physics. [DOI: 10.1063/1.1462041]

I. INTRODUCTION

Atomistic simulations of chemical reactions in extended complex systems such as biomolecules are one of the major challenges of computational chemistry. The description of chemical reactions requires highly accurate methods for electronic structure determination, which are also able to describe unstable intermediates, such as transition states. Moreover, since the majority of chemical processes are activated slow, simulations over long periods of time are needed. Density functional theory (DFT) based ab initio molecular dynamics techniques, such as the Car–Parrinello (CP) method,1,2 provide us with accurate computational tools to study chemical reactions in liquids and solids.3 However, biorelevant molecular environments, such as proteins, are usually too large for a straightforward application of this method, and the requirements on system size, accuracy, and duration of a run are difficult to reconcile.

This has led, already some time ago,4–6 to the idea of partitioning the system in a chemically active part, that is treated by quantum chemical methods (QM) and a larger environment, assumed to be chemically inert, that is modeled by a classical force field (MM).7 This approach is particularly appealing since the computational effort can be concentrated on the region where the chemical reaction is expected to happen (e.g., the active site of an enzyme), while taking advantage of the computational efficiency of classical force fields, that provide a more expedient description of the biomolecule far from the active site.

The QM subsystem can be described at different levels of quantum mechanical approximation applying semiempirical or ab initio methods. The generalization to a hybrid calculation is most natural for semiempirical methods and considerable experience already exists in this field.4–6,8–11 A similar development of fusing and adapting electronic structure methods and classical modeling techniques has been initiated in the ab initio world, using HF or DFT.12–20 Although similar to the problems encountered when using semiempirical methods, the compatibility problems in ab initio implementations are more critical as a consequence of the increased complexity and flexibility of the basis sets and of the larger difference in the level of approximation between the MM and the QM subsystems.

The central question in hybrid methods concerns the way in which the quantum and the classical subsystems are interfaced. As a consequence of the form of standard biomolecular force fields, the interactions coupling QM and MM degrees of freedom can be grouped in bonded and nonbonded. Bonded interactions arise when the QM/MM boundary cuts through a chemical bond of a molecule. In that case, one or more QM atoms are joined to MM atoms by incomplete covalent bonds which leave the QM atoms with unsaturated valence orbitals. The problem of interfacing across bonds has received special attention.21–28 The common solution is to “cap” the QM site with a link atom (frequently a hydrogen atom) or an empirically parametrized boundary atom, e.g., described by a suitable pseudopotential. An alternative is provided by the so-called frozen orbital approach, consisting in saturating the valence with suitable orbitals located on the MM atoms. These orbitals are included in the KS (or HF) Hamiltonian, but are not evolved during the simulation.26–28

However, such an approach, though physically sound, implies a significant increase in computational cost within a plane-wave (PW) based scheme.

The remaining bonded interactions, in particular angular and dihedral terms involving MM and QM atoms are kept into account by the classical force field.

Following the classification used in biomolecular force fields, the nonbonded interactions between the QM system and the MM atoms can be divided into steric and electro-
static environment effects. The steric nonbonded interactions due to the Pauli repulsion and the dispersion interactions are usually kept into account in a straightforward way by retaining the van der Waals interaction as described by the classical force field. The electrostatic interaction between the QM density and the point charges representing the charge distribution in the MM system often constitute the main environmental effect on the QM system and is technically more subtle.

Here, we will discuss a novel scheme to include electrostatic interactions between MM and QM subsystems in a PW-based CP molecular dynamics code. A natural choice for the nonbonded interaction Hamiltonian, extensively used in most of the advanced QM/MM approaches, is of the type,

$$H_{\text{nonbonded}} = \sum_{i \in \text{MM}} q_i \int dr \frac{\rho(r)}{r-r_i} + \sum_{i \in \text{MM}} \sum_{j \in \text{QM}} v_{\text{vdw}}(r_{ij}),$$

where $r_i$ is the position of the MM atom $i$, with charge $q_i$, $\rho$ is the total (electronic plus ionic) charge of the quantum system, and $v_{\text{vdw}}(r_{ij})$ is the van der Waals interaction between atom $i$ and atom $j$. The core charge of the QM atom $j$ is represented, in our approach, by a Gaussian charge distribution of magnitude $Z_j$ (the valence of the quantum atom $j$) and width $r_g$. Since the ionic charge distribution is explicitly coupled with the external field through Eq. (1), $r_g$ has to be chosen carefully in order to recover as close as possible the physical core charge distribution.

The form (1) for the electrostatic interaction Hamiltonian poses serious theoretical and technical problems, related to both its short range and its long range behavior. A first issue is related to the fact that positively charged classical atoms can act as traps for the electron if the basis set is flexible enough to allow for this. In fact, the Pauli repulsion from the electron cloud that would surround the classical atoms is absent, and therefore, the electron density is over-polarized, at short range, by an incorrect purely attractive potential, giving rise to the so-called electron spillout problem. This effect is particularly pronounced in a plane-wave basis-set approach, in which the electrons are fully free to delocalize, but can be of relevance also in schemes using localized basis sets, especially if extended basis sets with diffuse functions are used.

A second problem is related to the computational cost to compute the first term of the interaction Hamiltonian (1) within a plane-wave scheme. The number of operations that would be required for a direct evaluation of Eq. (1) is of the order of $N_s N_{\text{MM}}$, where $N_s$ is the number of real space grid points (of the order of $100^3$) and $N_{\text{MM}}$ is the number of classical atoms (usually of the order of $10^4$ or more in systems of biochemical relevance). In a real system, a straightforward computation of Eq. (1) would therefore increase the computational cost by several orders of magnitude. This serious bottleneck can be avoided employing techniques like the hierarchical multipole (HMP) method, an approach that has been developed in the framework of classical molecular dynamics simulations. A suitable extension of the HMP allows the calculation of the electrostatic potential on the grid at an affordable computational cost. This technique is accurate when used to compute the potential for a given configuration of MM atoms. However, in the current QM/MM implementation, the forces on the MM atoms due to the electron charge distribution are estimated as ordinary Coulomb forces from auxiliary charges located on the QM atoms (electrostatic potential derived charges), and this leads to a non-Hamiltonian description.

Here, we present a method to include the electrostatic interaction in PW-based QM/MM calculations that does not suffer from any of the problems outlined above. In particular, within our scheme (i) the short range interactions are accurately described without any spill-out of the electron density onto the MM atoms and without any need to reparametrize the classical force-field; (ii) the long range electrostatic interaction can be kept into account within a fully Hamiltonian scheme; (iii) the inclusion of the electrostatic coupling to the environment does not change the computational cost of the simulation significantly (for a straightforward implementation, the computational overhead is of the order of 20%–100%, and could be reduced further by employing multiple time step techniques in which the electrostatic interaction is updated on an ionic time scale).

The method we present here has been developed as a part of an interface between the Car–Parrinello code CPMD (Ref. 30) and the classical molecular dynamics package GROMOS96. A suitable decoupling technique is used to eliminate the effect of the periodic images of the QM charge density generated as a consequence of using a PW basis. The electrostatic interaction between classical atoms is kept into account by the P3M method.

II. SHORT-RANGE ELECTROSTATIC INTERACTIONS

In this section, we will discuss a method to treat non-bonded short-range interactions between QM and MM atoms within a fully Hamiltonian scheme. A consistent description of the electrostatic interaction between the QM subsystem and the nearest classical atoms is crucial in order to obtain an accurate prediction of the electronic and structural properties at the QM/MM interface. The MM atoms in the immediate vicinity of the quantum system are responsible for a large part of the polarization. For instance, the incorrect description of the energetics of a hydrogen bond between QM and MM atoms can lead to large errors that might frustrate any attempt to treat accurately the relevant but weaker longer range interactions. This problem has repeatedly been pointed out in the literature as a possible source of errors in QM/MM simulations. A direct inclusion of the Coulomb potential in the Kohn–Sham (or the Hartree–Fock) Hamiltonian as in Eq. (1) is widely applied in schemes based on localized basis sets. However, this leads to a model that is intrinsically unphysical since part of the electron density can artificially localize on positively charged MM atoms. In a localized basis set approach this problem might be less severe, but the unphysical nature of the interaction is present at any level of description, and is doomed to get worse if the basis set is extended. The severe shifts in the radial distribution functions and the large errors in the hydration enthalpies observed in QM/MM simulations of liquid water in which a single water is treated as a quantum fragment are pos-
sible manifestations of this effect. One suggested remedy to this problem is a reparametrization of the van der Waals radii of the classical atoms in order to compensate for this effect, but this ad hoc procedure does not eliminate the overpolarization of the electron cloud or the incorrect localization behavior of the electrons. Moreover, this approach does not always succeed, as demonstrated by Tu et al., who have reparametrized the force field in order to reproduce the structural properties of a QM/MM water dimer with no apparent improvement for the pair correlation functions of liquid water.

Here, we employ a computationally expedient alternative based on an empirical pseudopotential-like approach. The Coulomb potential is replaced with a suitable function \( v_j(r) \) (depending on the MM atom \( j \)) such that \( v_j(r) \) goes to \( 1/r \) for large \( r \) and to a finite value for small \( r \). The first term in the interaction Hamiltonian (1) is thus replaced by

\[
H_{el} = \sum_{j \in \text{MM}} q_j \int dr \rho(r) v_j(|r-r_j|).
\]

For a given functional form \( v_j(r) \), the forces on the MM atoms are obtained by a straightforward differentiation with respect to atomic coordinates [see Eq. (11)]. The forces can be computed together with the potential for the QM system in a single loop over the real space grid, without a significant computational overhead, leading to a fully Hamiltonian description.

The electronic and mechanical properties of the mixed QM/MM system depend critically on the choice of the function \( v_j(r) \). The most sensitive interactions are, in general, the direct contact interactions between QM and MM atoms, in particular the hydrogen bonds. In our approach, like in most of the other QM/MM approaches, we have chosen to retain a steric (van der Waals) interaction between the nuclei of the quantum part and classical atoms described by the classical force field. Given this choice, an accurate description of hydrogen bond distances and energetics can be obtained choosing a \( v_j(r) \) saturating to \( 1/r \) at a distance \( r_{c_j} \) from the MM atom \( j \), and smoothly going to a constant for small \( r \). In particular, we take

\[
v_j(r) = \frac{r^n}{r_{c_j}^{n+1} - r^{n+1}},
\]

where \( n = 4 \) and \( r_{c_j} \) is the covalent radius of the atom \( j \). This functional form resembles the form obtained by smearing the MM point charges into Gaussian charge distributions with finite width. Among other alternative choices for \( v_j(r) \), we tested functions with a repulsive core for small radius and functions going to zero for \( r \to 0 \). In all these cases, we obtained worse results. The influence of \( r_{c_j} \) on the pair correlation functions between QM and MM atoms has been probed by performing a QM/MM simulation of a quantum water molecule in a box of classical water. The QM subsystem is treated within a pseudopotential approach, employing Troulliers–Martins pseudopotentials. The wave functions are expanded in a plane wave basis set with a 70 Ry cutoff inside a cubic quantum box with an edge of 13 a.u.

The BLYP approximation is used for the exchange and correlation part of the Kohn–Sham Hamiltonian.

The radial distribution functions for various choices of the cutoff radii \( r_{c_j} \) are summarized in Figs. 1(a) and 1(b) for the oxygen–hydrogen and in Fig. 1(c) for the oxygen–oxygen pair correlation functions. All simulations were performed starting from a thermalized box of 256 classical SPC water molecules at normal density and at a temperature of 300 K. Data have been collected for 10 ps after 5 ps of QM/MM thermalization. The influence of the functional form of \( v_j(r) \) on the bonding properties of the system can be dramatic. If, e.g., \( r_{c_j} = 0.8 \) Å is chosen for all the classical atoms the first peak in the oxygen–hydrogen pair correlation function disappears, indicating that the hydrogen bond be-

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**FIG. 1.** Pair correlation functions for a quantum water in a box of classical (SPC) water molecules compared with full classical SPC water (continuous line with circles) and full quantum (Ref. 40) (continuous line with diamonds) results. Continuous line: \( r_{c_j} \) in Eq. (5) for oxygen and hydrogen are 0.8 and 0.4 Å, respectively; dashed line: \( r_{c_j} \) for oxygen and hydrogen are 0.8 and 0.8 Å; dotted line: \( r_{c_j} \) for oxygen and hydrogen are 1.4 and 0.8 Å. (a) Quantum oxygen–classical hydrogen pair correlation function. (b) Quantum hydrogen-classical oxygen pair correlation function. (c) Quantum oxygen–oxygen pair correlation function.
tween the quantum oxygen and the classical hydrogen is essentially lost and the solvation structure vanishes almost entirely. If \( r_e \) is chosen to be equal to the van der Waals radius (\( \sim 0.8 \) Å for hydrogen and \( \sim 1.4 \) Å for oxygen) also the oxygen–oxygen peak is strongly shifted and smeared out, showing that with this choice, the quantum water molecule interacts too weakly with the classical water. The correlation functions computed without modification of the Coulombic interactions cannot be consistently defined within our approach, since, if this functional form is chosen a fraction of the electron density localizes on the classical hydrogens. Additionally, if no smearing is applied to the Coulombic interaction, the electrons heat up significantly during the simulation (see Fig. 2), showing that the system is unstable with a typical choice for the fictitious mass of the electrons. Pair correlation functions consistent with the full quantum\(^{40}\) and the full classical (SPC) results could instead be obtained by choosing \( r_e \) sufficiently close to the covalent radius (i.e., \( \sim 0.4 \) Å for hydrogen and \( \sim 0.7 \) Å for oxygen), as shown in Fig. 1. With this choice, the position and the size of the peaks predicted by the QM/MM model is in close agreement with the classical and the full QM results. Moreover, we have checked that the pair correlation functions are unchanged (within the noise of a limited simulation of 10 ps) if \( r_e \) is changed throughout a range between a factor of 0.6–1.2 of the covalent radius.

The consistency of our approach has been further checked by computing the pair correlation function of a chloride ion solvated in SPC water (the QM system in this case consists of the Cl\(^-\) ion alone). The chloride ion is described by a Troulliers–Martins pseudopotential\(^ {37}\) retaining seven electrons in valence, with a cutoff of 70 Ry in a simple cubic box of 12 a.u. Due to the excess negative charge, this system is particularly sensitive with respect to possible spill-out problems. The first and second peak of the Cl–H pair correlation function \( g_{\text{Cl-H}}(r) \), and the first peak of the Cl–O pair correlation function \( g_{\text{Cl-O}}(r) \) are located at 2.35, 3.7, and 3.3 Å, respectively. The corresponding experimental values, computed with a pulsed neutron diffraction technique,\(^ {41}\) are 2.29, 3.66, and 3.25 Å. Hence, our QM/MM approach reproduces the experimental positions of the first maxima of the chloride ion–water pair correlation function with an accuracy of \( \sim 0.05 \) Å. The hydrogen coordination number, as obtained with the same procedure employed in the experimental study\(^ {41}\) (i.e., fitting the Cl–H pair correlation between 1 and 3.1 Å with a single Gaussian) is 6.6. This compares with an experimental coordination number of 5.8±0.5, and with values computed using classical force fields ranging between 5.7 and 11.7 (Ref. 42, and references therein).

As a final test case, we investigated a quantum ammonium ion solvated in a box of 1720 classical SPC water molecules. The pair correlation function obtained with our QM/MM approach are extremely close to the full ab initio results\(^ {43}\) (see Fig. 3). In particular, the position of the first peak, the first minimum and the second peak of the \( H_{\text{NH}}-O_{\text{W}} \) pair correlation function are identical within 0.05 Å if calculated with a QM/MM or a fully ab initio approach (see Fig. 3).

In conclusion, our choice for the modified Coulombic interaction [Eq. (3)], reproduces correctly the structural properties of a quantum water molecule solvated in classical water and the solvation structure both of a negatively charged system (the chloride ion in aqueous solution) and of a positively charged system (the ammonium ion in water) with the same choice of parameters.

III. LONG RANGE ELECTROSTATIC INTERACTION

A direct computation of the interaction Hamiltonian (2) with the summation running over all the charges of the MM system would be too expensive within a plane-wave based approach. In this section, we introduce a method that allows, within a fully Hamiltonian scheme, an accurate and computationally efficient evaluation of Eq. (2). In the coupling scheme we present in this article, the Coulombic electrostatic field is included exactly only for a set of MM atoms in the vicinity of the QM system. This set of atoms (NN atoms) is defined in such a way as to include all (non-neutral) atoms belonging to charge groups\(^ {3} \) with at least one atom inside a shell of thickness \( r_s \) around any quantum atom. Hence, care is taken that charge groups are included (or excluded) as a whole from the direct interaction with the quantum system.

The electrostatic field on the MM atoms that do not belong to the NN set is calculated by a multipolar expansion of
the full interaction given in Eq. (2). In fact, since the charge density of the quantum system is localized (e.g., inside a sphere of radius \( R_q \) around the geometrical center of the quantum system), up to quadrupolar order, the electrostatic field due to \( \rho \) at the position \( r_j \) of the MM atom is given by

\[
\int \frac{d\rho(r)}{|r-r_j|} = C \frac{1}{|r-r_j|} + \sum \frac{D^a}{|r-r_j|^3} + \frac{1}{2} \sum_{\alpha} Q^{\alpha\beta} \frac{(r^\alpha - \bar{r}^\alpha)(r^\beta - \bar{r}^\beta)}{|r-r_j|^5} + \mathcal{O}\left(\frac{R_q}{|r-r_j|}\right)^4,
\]

where \( \bar{r} \) is the origin of the multipolar expansion (in our implementation the geometrical center of the quantum system) and \( C, D^a, \) and \( Q^{\alpha\beta} \) are the total charge, the dipole, and the quadrupole of the quantum charge distribution \( \rho \). \( C, D^a, \) and \( Q^{\alpha\beta} \) are, respectively, given by

\[
C = \int d\rho(r),
\]
\[
D^a = \int d\rho(r) (r^a - \bar{r}^a),
\]
\[
Q^{\alpha\beta} = \int d\rho(r) \left[ 3(r^\alpha - \bar{r}^\alpha)(r^\beta - \bar{r}^\beta) - \delta^{\alpha\beta}|r-\bar{r}|^2 \right],
\]

where Greek indices are assumed to run from 1 to 3. Since for \( |r-r_j| > R_c \), \( v(r-r_j) = (1/|r-r_j|) \left( 1 + \mathcal{O}(r_c/|r-r_j|)^2 \right) \) for all atoms \( j \) outside the NN set, using Eq. (4) the electrostatic interaction (2) can be expressed, neglecting terms of the order of \( \mathcal{O}(R_q/\min_{j \in NN}|r_j-r_i|)^4 \), as

\[
H_R = \sum_{j \in NN} q_j \int d\rho_c(r) v_j(|r-r_j|) + H_u,
\]

where \( H_u \) is given by

\[
H_u = C \sum_{j \in NN} q_j x_j + D^a \sum_{j \in NN} \frac{q_j x_j}{r_j} + \frac{1}{2} \sum_{\alpha} Q^{\alpha\beta} \sum_{j \in NN} \frac{q_j x_j^\alpha}{r_j^\beta} x_j^{\alpha \beta}
\]

with

\[
x_j^\alpha = x_j^\alpha - \bar{x}^\alpha.
\]

Since the MM atoms are divided, except for physically charged groups, into globally neutral clusters,\(^5\) the error can be reduced further using two different cutoffs for uncharged and charged units. If a sufficiently large cutoff is used for the comparably few charged groups, the first term neglected in the multipolar expansion is an octupole–dipole term with the neutral groups at \( R_c \), hence the error is of the order \( \mathcal{O}(R_q/(R_c + R_q))^4 \). The convergence of \( H_u \) to the Hamiltonian (2) can be systematically improved by including multipoles of higher order with very small additional computational cost.

The only free parameter in the present approach is the thickness \( R_c \) of the shell of MM atoms explicitly coupled to the quantum system. The convergence of the results with respect to \( R_c \) can be checked directly comparing the results obtained for finite \( R_c \) with the values obtained with the full interaction Hamiltonian (2).

As a test case, we have considered a QM/MM calculation of the mouse prion protein\(^\text{23} \) in solution with a single peptide unit (Gly126) as the QM part. The system is terminated by three dummy carbon atoms represented by monovalent pseudopotentials,\(^\text{25} \) as shown in Fig. 4 (one located on the \( C_p \) of the side chain, an aspartate in this particular case, and the other two located respectively on a \( C_a \) and on the backbone carbonyl carbon atom of the following peptide unit). The prion protein is a good test system to probe the performance of an electrostatics coupling scheme, since it has a strongly dipolar charge distribution and hence long range electrostatic effects have a sensitive influence on the properties of the system:\(^\text{45} \) For an arbitrarily chosen snapshot configuration of a MD run, we have computed, as a function of \( R_c \), the total energy \( E_{\text{tot}} \), and the dipole \( D_c \) of the system. In particular, the values at finite \( R_c \) are compared with the ones obtained for very large \( R_c \), for which the full protein is explicitly coupled to the quantum system by Eq. (2). Moreover, denoting by \( \rho_{R_c} \) and by \( \rho_{R_c=\infty} \) the density for the finite and very large \( R_c \), we have computed the charge polarization

\[
P = \int d\rho |\rho - \rho_{R_c=\infty}|.
\]

The differences in energy, dipole moments, and polarization are a measure of the approximation that is done when using Hamiltonian (6) instead of Hamiltonian (2). The results are reported in Table I. As it is apparent, \( E_u \) and \( D_u \) converge quickly, as a function of \( R_c \), to the value obtained using the full Hamiltonian (2), and \( P_u \) converges rapidly to zero. For a comparison, we calculate the total energy \( E_{\text{mc}} \), the dipole \( D_{\text{mc}} \) and the charge polarization \( P_{\text{mc}} \) in the case in which the long range interaction is kept into account by a classic Coulomb interaction. In this case \( H_u \) in Eq. (6) is replaced by

\[
H_{\text{mc}} = \sum_{i \in \text{NN}} \sum_{j \in \text{QM}} \frac{q_i q_j}{r_{ij}},
\]

i.e., the long range electrostatic interaction is treated within a “mechanical coupling” scheme\(^7\) (\( q_j \) is the force field
TABLE I. Total energies $E$, dipole $D$, and polarization $P$ [as given by Eq. (8)] as a function of the cutoff radius for the explicit electrostatic interaction $R_c$ for the system of Fig. 4. Values labeled ‘‘lr’’ and ‘‘mc’’ are, respectively, obtained if the long range interaction is described by Eqs. (7) and (9). Energies are in a.u. $10^{-5}$. The zero of the energy and the reference value for the density are defined by the value of the total energy and of the density obtained if an interaction Hamiltonian of the form (2) is used. $R_c$ is in a.u. Dipoles are in Debye. $P$ in elementary charge units is calculated as given by Eq. (8).

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<th>$E_{mc}$</th>
<th>$D_u$</th>
<th>$D_{mc}$</th>
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charge of the QM atom $j$). As it is apparent in Table I, using a mechanical coupling scheme for the interaction between the QM atoms and the MM atoms not included in the NN set implies a significant error on the total energy, dipole moment, and charge polarization of the system even for rather large values of the cutoff radius $R_c$.

IV. POTENTIAL AND FORCES ON THE ATOMS

In our approach, the nonbonded interaction between the QM and the MM system is described by an Hamiltonian of the form,

$$ H_{\text{nonb}} = H_{\text{el}} - \sum_{i,j \in \text{QM}} \frac{Z_i q_j}{r_{ij}} + \sum_{i,j \in \text{QM}} v_{\text{vdw}}(r_{ij}), $$

with $H_{\text{el}}$ given by Eq. (6). Energy conserving dynamics can be performed if the potential and the forces are calculated consistently. The potential is obtained by taking the functional derivative of Eq. (6) with respect to $\rho$,

$$ V(r) = \frac{\delta H_{\text{el}}}{\delta \rho} = \sum_{j \in \text{NN}} q_j \rho_j(|r-r_j|) + V_{\mu}(r), $$

(10)

with

$$ V_{\mu}(r) = \frac{\delta H_{\mu}}{\delta \rho} = \sum_{j \in \text{NN}} \frac{q_j}{\tau_j} + \sum_{\alpha} \frac{q_j}{\tau_j} \left[ \frac{3}{2} (r^\alpha - \bar{r}^\alpha) (r^\beta - \bar{r}^\beta) - 3 \delta^\alpha \delta^\beta |r-\bar{r}|^2 \right] $$

$$ + \sum_{j \in \text{NN}} \frac{q_j}{\tau_j} \tau_j^{\alpha} \tau_j^{\beta}. $$

Since this potential is explicitly included in the Kohn–Sham Hamiltonian, the electron density is polarized up to any multipolar order by the atoms in the NN set and up to quadrupolar order by the rest of the MM atoms.

The forces on the atoms are obtained by taking the derivative of Eq. (6) with respect to the atomic positions. For $j$ in the NN set the forces are given by

$$ F_j^\mu = q_j \int dr \rho(r) g_j(|r-r_j|) \frac{r^\alpha - \bar{r}^\alpha}{|r-r_j|}, $$

(11)

where $g_j(r) = d\rho_i/dr$. The forces on a MM atom not belonging to the set NN is

$$ F_j^\gamma = -q_j \left[ \frac{C}{\tau_j} - 3 \frac{1}{\tau_j} \sum_{\alpha} D^\alpha \tau_j^\alpha - \frac{1}{2} \frac{1}{\tau_j} \sum_{\alpha\beta} Q^{\alpha\beta} \tau_j^\alpha \tau_j^\beta \right] \tau_j^\gamma $$

$$ + \frac{D^\gamma}{\tau_j} + \frac{1}{\tau_j} \sum_{\alpha} Q^{\alpha\gamma} \tau_j^\alpha. $$

Finally, the forces on the quantum atoms deriving from Eq. (7) are (independently of the atom)

$$ F_j^\gamma = \frac{1}{N_Q} \left[ -\frac{5}{2} \sum_{\alpha} Q^{\alpha\beta} \sum_{k \neq \text{NN}} \frac{q_k}{\tau_k} \tau_k^\alpha \tau_k^\beta + \sum_{\alpha} Q^{\alpha\gamma} \sum_{k \neq \text{NN}} \frac{q_k}{\tau_k} \tau_k^\alpha \tau_k^\beta \right], $$

(13)

where $N_Q$ is the number of quantum atoms. Moreover, the quantum ions are subject to the forces due to the potential (10). If $\rho_{\text{G}}(|r-r_j|)$ is the Gaussian density used to represent the core charge distribution of the quantum atom $j$, we have

$$ F_j^a = -\int dr V(r) \frac{d\rho_{\text{G}}}{dr} \frac{r^\alpha - \bar{r}^\alpha}{|r-r_j|}. $$

The computation of the forces on the atoms and of the potential due to Eq. (6) is computationally relatively inexpensive. The computational bottleneck is the evaluation of the first term in Eq. (6), requiring the calculation of the distances between every grid point and all the NN atoms. The evaluation of the potential and the forces derived from the second term in Eq. (6) is instead inexpensive, since it requires only the calculation of the distances between all MM atoms and all grid points from a single point (the geometrical center of the quantum system).

If the long range coupling scheme described in Sec. III is employed, the computational price of a QM/MM calculation becomes comparable to the price of a pure QM calculation on the same quantum system. The computational overhead ranges between ~20% for large quantum systems to ~100% for very small QM systems. For instance, for the ammonium ion in aqueous solution the CPU time for a time step is 3.7 s on a 4 processor IBM SP (Power 2). The computation of the MM forces requires 2.1 s on a single CPU. The other 3 CPUs compute the quantum forces in a total of 3.4 s, 1.5 s are spent in the computation of the electrostatic interaction and 1.9 s in the evaluation of the QM forces. The QM/MM calculation on a single peptide unit described in Sec. II requires 37.3 s for a time step on a single 700 GHz Pentium III processor, 20.2 s for the quantum forces, 12.5 s for the electrostatic interaction and 4.6 s for the MM forces.
The correctness of the implementation can be directly verified by monitoring the conservation of energy for MD simulations. Some typical examples are shown in Fig. 5. In these cases the drift is only $10^{-6}$ a.u. per ps and per particle.

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