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REGULAR ARTICLE

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Ab initio quantum mechanical charge field (QMCF) molecular dynamics: a QM/MM – MD procedure for accurate simulations of ions and complexes

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Abstract A new formalism for quantum mechanical / molecular mechanical (QM/MM) dynamics of chemical species in solution has been developed, which does not require the construction of any other potential functions except those for solvent–solvent interactions, maintains all the advantages of large simulation boxes and ensures the accuracy of ab initio quantum mechanics for all forces acting in the chemically most relevant region. Interactions between solute and more distant solvent molecules are incorporated by a dynamically adjusted force field corresponding to the actual molecular configuration of the simulated system and charges derived from the electron distribution in the solvate. The new formalism has been tested with some examples of hydrated ions, for which accurate conventional ab initio QM/MM simulations have been previously performed, and the comparison shows equivalence and in some aspects superiority of the new method. As this simulation procedure does not require any tedious construction of two-and three-body interaction potentials inherent to conventional QM/MM approaches, it opens the straightforward access to ab initio molecular dynamics simulations of any kind of solutes, such as metal complexes and other composite species in solution.

1 Introduction

As most of the relevant chemical reactions take place in solution, reliable methods for an accurate theoretical treatment of chemical species in solution have always been in strong demand. The crucial role played by ions and metal complexes in biology [1,2] underlines the importance of a detailed knowledge of structure and dynamics of these species in (aqueous) solution [3–6].

In the past decades numerous methods have been developed to increase the accuracy of statistical simulations of condensed systems, in particular liquids and solutions, beyond the level of classical pair (and eventually three-body corrected) potential-based molecular dynamics (MD) and Monte Carlo methods. Due to the computational power needed by the introduction of quantum mechanical energy and force calculations, compromises had to be sought through multiregion approaches, for example, the ONIOM method implemented in the GAUSSIAN programme [7,8].

Car–Parinello dynamics [9] realise this compromise by the usage of a simple density functional and the reduction of the investigated system to a moderate size of 100–200 atoms. Hybrid quantum mechanical/molecular mechanical (QM/MM) methods [10–13] reduce the computational effort to an affordable extent by treating only a sub-region of the system by ab initio or density functional theory (DFT) quantum mechanics, and the remaining system by classical potentials.

Experience collected during the past few years with the application of such methods to solvated ions has shown that a low-level quantum mechanical treatment is not sufficient for a reliable description of these systems, and that Hartree–Fock level calculations with double zeta plus polarisation basis sets seem to be the lower limit for the method, while the full inclusion of the first and sometimes even the second solvation shell in the QM region is mandatory [6,14–16].

The formalism of QM/MM simulations requires, besides the quantum mechanical calculation of the interactions inside the QM region and the force-field calculations within the MM region, the evaluation of interactions between species inside and outside the QM region, which is usually achieved with the help of ab initio constructed pair and three-body potential functions or on the basis of empirical force fields. The construction of new potential functions is a time-consuming and tedious task, implying the evaluation of several thousands if not ten thousands of single points on the energy surfaces for all interacting species pairs and triples, followed

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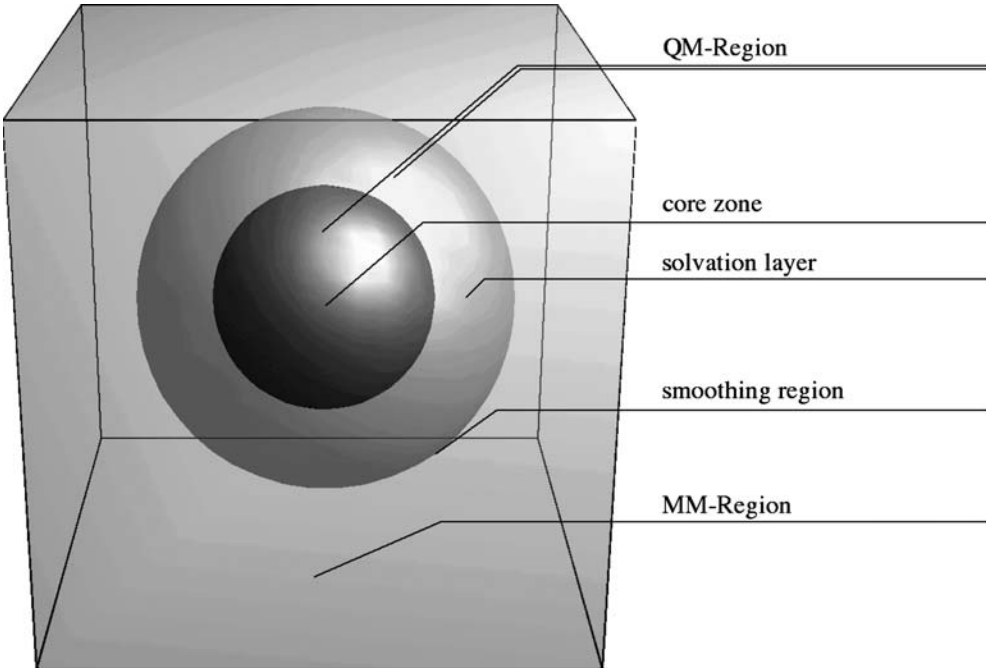

Fig. 1 Definition of the quantum mechanical (QM) and molecular mechanical (MM) regions in the QMCF approach

by the search of suitable analytical functions representing these interactions.

The procedure presented here aims at two targets in order to improve the quality of ab initio QM/MM simulations: first, the accuracy should be pushed to the limits feasible with present (and near future) computational facilities; second, the need for the construction of new potentials for every new species to be introduced – except new solvents – should be eliminated, thus giving a wide and direct access to numerous systems of interest for complex and solution chemistry as well as biochemistry, in paticular ions forming solvates or solvated complexes with other ligands.

The formalism proposed attempts to achieve these goals by an extension of the QM region to a moderately larger extent, as found desirable by simulations of some ions in water [6], with a simultaneous use of quantum mechanically calculated data for the continuously changing charge distribution in the solute and its first surrounding solvent layer, and by the evaluation of all interactions of the solute with more distant solvent molecules on the basis of a dynamic charge field.

Conventional two-shell QM/MM simulations have proven in the past to reach high accuracy for structural details and ultrafast solution dynamics of pure solvent [17] and hydrated ions [6,14–16]. A satisfactory reproduction of these results or a possible further improvement could be seen as a crucial test for the quality of the formalism proposed in this paper.

2 Methodical framework of the QMCF MD approach

The basic principle of the QM/MM formalism [10–13], that is, the partition into a QM and a MM region is maintained. The main difference of the methodical framework presented here lies in the definition and size of the QM region, which now consists of two subregions (Fig. 1), and the treatment of interactions/forces between the "inner" QM subregion and the MM region:

$$F_J^{\mathrm{core}} = F_J^{\mathrm{QM}} \tag{1}$$

$$F_J^{\mathrm{layer}} = F_J^{\mathrm{QM}} + \sum_{I=1}^{\mathrm{M}} F_{IJ}^{\mathrm{BJHnC}} \tag{2}$$

$$F_J^{\mathrm{MM}} = \sum_{\substack{I=1\\ I\neq J}}^{M} F_{IJ}^{\mathrm{BJH}} + \sum_{I=1}^{N_1+N_2} \frac{q_I^{\mathrm{QM}} \cdot q_J^{\mathrm{MM}}}{r_{IJ}^2} + \sum_{I=1}^{N_2} F_{IJ}^{\mathrm{BJHnC}} \tag{3}$$

where F_J^{core} (Eq. 1) corresponds to the quantum mechanical force acting on a particle J in the core zone, F_J^{layer} to the forces acting on a particle J located in the solvation layer and F_J^{MM} to the forces acting on a particle J in the MM region. In the latter case, these forces are composed – for the solvent water – of the forces of the BJH-CF2 [18,19] water model augmented by the Coulombic forces exerted by all atoms in the core region (N_1) and the solvation layer (N_2), and the non-Coulombic forces exerted by the atoms in the solvation layer (N_2) (Eq. 3). Due to this formalism the QM forces in the solvation layer have to be supplemented by the non-Coulombic forces as well (Eq. 2.). The electrostatic interaction between atoms located in the QM regions (N_1 and N_2) and the particles in the MM is incorporated via a perturbation term of the core Hamilton operator:

$$V' = \sum_{J=1}^{M} \frac{q_{\mathrm{J}}}{r_{\mathrm{iJ}}} \tag{4}$$

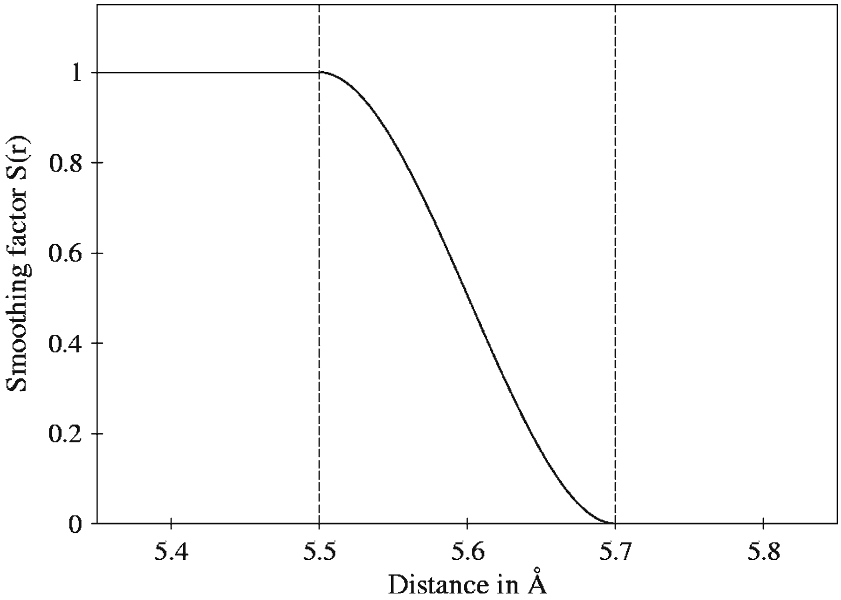

Fig. 2 Smoothing function applied between 5.5 and 5.7 Å

where M is the number of atoms in the MM region, q_J are the partial charges of these atoms (in this case the BJH-CF2 charges).

To ensure a smooth transition of solvent molecules moving between the solvation layer and the MM region, a smoothing function has to be applied to the atoms of all molecules located in this smoothing region:

$$F_j^{\text{Smooth}} = S(r) \cdot \left(F_j^{\text{layer}} - F_j^{\text{MM}}\right) + F_j^{\text{MM}} \tag{5}$$

where,

$$S(r) = 1, \quad \text{for r} \leq r_1$$
$$S(r) = \frac{(r_0^2 - r^2)^2 (r_0^2 + 2r^2 - 3r_1^2)}{(r_0^2 - r_1^2)^3}, \quad \text{for } r_1 < r \leq r_0 \tag{6}$$
$$S(r) = 0 \quad \text{for} \quad r > r_0$$

r is the distance of a given solvent molecule (centre of mass) from the centre of the box, r_0 the radius of the QM region and r_1 the inner border of the smoothing region (usually $r_0 - 0.2$ Å; Fig. 2).

The core region contains the solute, which can be any type of molecule or composite species, for example, a metal ion with identical or different ligands, and the solvation layer consists of one complete layer of solvent molecules surrounding the solute. In the simple case of a hydrated ion, this would correspond to an ion plus two complete hydration spheres in the QM region, an example for a complex species would be $[\text{Fe(CN)}_6]^{3-}$ (core region) with one full hydration layer (solvation layer). Outside this region, the remaining solvent is treated by molecular mechanics, that is, by suitable potential functions, which are already available for many common solvents. A smoothing function as being used in conventional QM/MM simulations [6] ensures a continuous and steady transition between the quantum mechanically treated solvation layer and the MM region. As smoothing takes place at a relatively large distance to the solute, transitions are less abrupt than in conventional QM/MM procedures, also because the influence of the MM region on the layer part of the QM region is fully included within the QMCF formalism. The size of the 'core' region is set to include the complete solute including all solvent ligands directly bound to it. The 'layer' region is sized to include a further complete solvation shell. In the case of the ions treated in the present study this means a diameter of 5.0–6.5 Å for the 'core' and 10.0–11.5 Å for the total QM region.

2.1 Evaluation of energies and forces

Inside the QM region, all interactions are evaluated by means of quantum mechanics, in the examples presented here at ab initio Hartree–Fock level with DZP basis sets. Other levels of theory could be applied as well, for example, MP/2 [20] (with much higher computational effort) or a suitable density functional method, such as B3LYP [21] (with computing times similar to HF). Interactions between the outer solvation layer inside the QM region and solvent molecules in the MM region, and interactions between solvent molecules within the MM region are treated by the solvent – solvent potential functions, making use of the smoothing function as outlined before. When calculating the Coulombic interactions between solvent molecules in the layer region and those in the MM region, the actual quantum mechanically evaluated charges obtained from population analysis are assigned to all atoms in the QM layer region (accounting also for the influence of the point charges in the MM region).

Among the numerous methods of population analysis the QMCF formalism has been primarily examined employing the most common Mulliken method with pure water as test system. This test has shown that the Mulliken charges in the

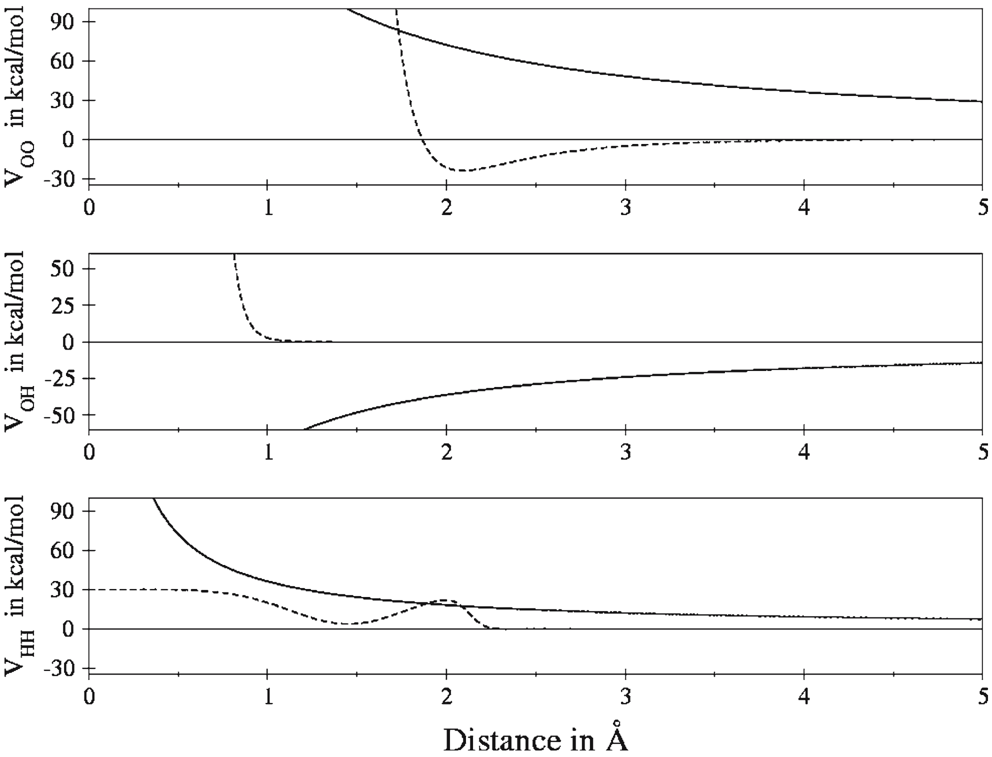

Fig. 3 Coulombic (*solid line*) and non-Coulombic (*dashed line*) interaction potentials of the BJH-CF2 water model [18,19]

QM regions fluctuate between −0.67 and −0.78 for oxygen and from +0.33 to +0.40 for hydrogen, respectively. Hydrogens of the same water molecule generally have different partial charges due to different hydrogen bonding. The average charges lead to a somewhat higher dipole moment of the individual water molecules than for isolated gas phase molecules, which is quite realistic for liquid water. The charges of the ions show a considerable fluctuation in charge transfer. For instance the partial Mulliken charge of Al(III) lies between 2.4 and 2.6, for Mn(II) and Cu(II) the corresponding values fluctuate between 1.2 and 1.5.

The aforementioned test simulation for pure water has shown that for the given basis sets the scheme using Mulliken population and the BJH-CF2 water model leads to a satisfactory over-all description of several microscopic and macroscopic properties of water. Further tests of the QMCF approach with other population analysis methods and basis sets are planned, however.

Solvent transitions between QM and MM regions are allowed and, due to the smoothing function, occur without any discontinuity of energies and forces. In this context, the use of the flexible BJH-CF2 water model is also important for reasons of consistency with the fully flexible molecular geometries in the QM region. Any molecule transiting to the MM region can retain its geometry as initial configuration in the MM region.

The main difference to conventional QM/MM techniques concerns the evaluation of interactions between solvent molecules in the MM region and the solute, that is, the inner 'core' of the QM region. Due to the distance of this 'core' to the MM region, all short-range terms of any type of interaction potentials, which usually consist of a Coulombic term plus a series of $r^{-n} (n > 3)$ terms, sometimes also an exponential term, become negligibly small, and in most cases are already eliminated by the usual cut-offs in typical simulation protocols. The illustration of the Coulombic and non-Coulombic interaction potentials of the BJH-CF2 model are depicted in Fig. 3. It can be seen that the non-Coulombic interactions are negligible at long distances, and only the Coulombic potentials remain relevant.

These Coulombic interactions can be evaluated simply from the point charges assigned to the molecules/atoms in the MM region and the partial charges on the atoms of the solute. This approach has been utilised already in a simple way some decades ago [22] and is currently applied in some QM/MM simulation protocols for organic and biomolecules [23]. In the present case this corresponds to an electrostatic description by a dynamically changing field of point charges, which varies according to the movements of atoms inside the QM region(s) and molecules in the MM region in the course of the simulation. As a further improvement of this charge field, point charges assigned to atoms in the QM region will be redefined in every step of the simulation according to the new configuration, following each quantum mechanical calculation step. This ensures the continuous adaptation of the dynamical charge field to all polarisation and charge transfer effects within solute and surrounding solvent layer according to the dynamical changes of the solute's structure (which are much more significant than the small changes eventually occurring at the solvent molecules in the MM region, which are not considered in this formalism). For both QM regions, the influence of the charges of the molecules in the MM region is taken into account by incorporating the charges of their atoms as additional, perturbational term into the core Hamiltonian, representing the outside solvent influence at molecular level according to the actual location and orientation of the solvent molecules (Eq. 4).

All important solvent exchange processes take place within the QM region, and thus the relevant dynamics are evaluated with the accuracy of quantum mechanically calculated forces.

By this approach, the treatment of solutes of very different nature becomes a much more simple and straightforward process, as only potential functions for solvent–solvent interactions are needed, whereas all other interactions are dealt with at the quantum mechanical level, which also means at much higher accuracy than molecular mechanics potentials could achieve. The application of all other conditions of a MD simulation (large number of solvent molecules, periodic boundary condition, minimal image convention and long-range force corrections by reaction field) ensure that the system corresponds to the condensed, liquid state. It should not be concealed, however, that the inclusion of a relatively large number of species in the QM regions pushes the computational effort to a much higher demand than one-shell QM/MM molecular dynamics. On the other hand, the constant and rapid progress of processor speed has made simulations of the ab initio QM-CF-MD type already feasible and will soon allow the treatment of fairly complex systems of solution chemistry and biochemistry.

The programme code (TCI-QSIM) includes an interface to the TURBOMOLE [24–27] programme, which allows a parallelised performance of the quantum mechanical calculations. All simulations reported here were performed on Linux clusters with four to eight (according to optimal parallelisabilty) 2.8-GHz processors. The other details of the molecular dynamics simulation protocol were the same as in previous simulations [6]: elementary box with one ion and 499 water molecules, periodic boundary condition, NVT ensemble with temperature control by the Berendsen algorithm [28], time step of 0.2 fs, general predictor–corrector algorithm, cut-off for non-Coulombic interactions in the MM region of 5 and 3 Å for O–H and H–H, respectively, and reaction field correction for long-range Coulombic interactions. For the solvent water, the BHJ-CF2 [18,19] potential was used, as it ensures by its intramolecular term the full flexibility of water molecules transiting from the QM into the MM region.

The DZP basis sets for metal ions and water for the QM region were the same as employed in previous simulations [15, 16,29]. The starting configurations were taken from equilibrated two-shell QM/MM MD simulations of the respective ions. After 2–3 ps of equilibration at least 5 ps of sampling were performed.

The CPU time required for one simulation amounts to 6 – 8 months and thus, the net computing time for all reported simulations amounts to approximately 50 months, using on average six processors in parallel for each simulation.

3 Test results and evaluation of the method

Hydrated ions, for which conventional ab initio QM/MM-MD simulations including two hydration shells in the QM region with a well-established simulation protocol have been performed [15,16,29], were investigated using the new ab initio QMCF approach.

Testing of the new method has been performed in two steps. In the first step, the QMCF scheme was applied to Mn(II) [29] and Cu(II) [15] still employing the fixed MM charges of solute and solvent molecules in the evaluation of the Coulombic forces acting between central ion and water molecules in the first and second hydration shell – being part of the QM region – and the surrounding bulk. This procedure corresponds to the employment of a fixed charge field, but with the possibility to avoid the construction of specific solute–solvent interaction potentials, and allows for a direct comparison of the QMCF scheme with conventional QM/MM molecular dynamics.

In the second step, dealing with Al(III) and Cu(II) as test examples, the previously outlined consideration of continuously changing charges computed quantum mechanically via Mulliken population analysis [30] was invoked, the charges of the MM region were included as perturbation into the Hamiltonian of the QM regions. This second step allows to determine the significance of the fluctuations of charges and polarisations due to the movements of all particles in the system.

Tables 1 and 2 show a comparison of characteristic results for Mn(II) and Cu(II) for different ab initio QM/MM simulation methods, the first conventional including only the first hydration shell into the QM region and applying a three-body correction function for the second hydration shell (upto 6 Å), the second conventional, including also the second shell into the QM region and the third one employing the new QMCF formalism (step 1). Figures 4 and 5 show the corresponding ion–oxygen radial distribution functions (RDF). For the two-shell QM/MM MD simulation of Mn(II) the same simulation protocol was employed as for the QMCF MD simulations. However, the treatment of the forces refers to the QM/MM MD formalism, including the same smoothing functions employed in the two-shell simulations of Al(III) [16] and Cu(II) [15].

In the case of Mn(II) (Table 1) one observes nearly no difference between the three applied methods for the first hydration shell, whereas the second shell was difficult to characterise with the one-shell-only method and showed a somewhat unusual shape and extension even after inclusion of the second shell (Fig. 4). Introduction of the new formalism (step 1) smoothens the RDF in this region and reduces the second shell coordination number to a very reasonable value of 14 ligands. A similar effect is observed in the case of Cu(II), where the QMCF procedure (step 1) leads to a better characterisation of the second shell without the ambiguous peak at 5.2 Å (Table 2, Fig. 5), probably caused by the transition between QM and MM region, which is more abrupt in the conventional formalism than in the QMCF approach.

Table 1 Maxima r_M and minima r_m of the Mn(II)–O radial distribution function in Å and average coordination numbers of the respective shells

	$g_{Mn(II)-O}$						
	r_{M1}	r_{m1}	r_{M2}	r_{m2}	$CN_{av,1}$	$CN_{av,2}$	Ref.
One-shell QM/MM simulation	2.3	2.7	4.4	5.2	6.0	15.9	[29]
Two-shell QM/MM simulation	2.2	2.8	4.9	4.5/5.9^a	6.0	26.1	This work
QMCF simulation – step 1	2.2	2.8	4.6	5.2	6.0	13.7	This work

^{a} ambiguous shape of the second shell peak (Fig. 4)

Table 2 Maxima r_M and minima r_m of the Cu(II)–O radial distribution function in Å and average coordination numbers of the respective shells.

	$g_{Cu(II)-O}$						
	r_{M1}	r_{m1}	r_{M2}	r_{m2}	$CN_{av,1}$	$CN_{av,2}$	Ref.
One-shell QM/MM simulation (HF)	2.05/2.2	2.8	4.6	5.3	6.0	11.7	[34]
One-shell QM/MM simulation (MP/2)	2.05/2.35/2.5	2.7	4.6	5.3	6.0	10.4	[31]
Two-shell QM/MM simulation (HF)	2.0/2.15/2.3	2.6	4.2	5.0	6.0	12.7	[15]
QMCF simulation – step 1 (HF)	2.0/2.15/2.3	2.9	4.4	5.5	6.0	16.7	This work

The 2nd/3rd value for r_{M1} corresponds to the slight shoulders reflecting the Jahn–Teller distortions of the first hydration shell, determined by differential analysis of the first peak

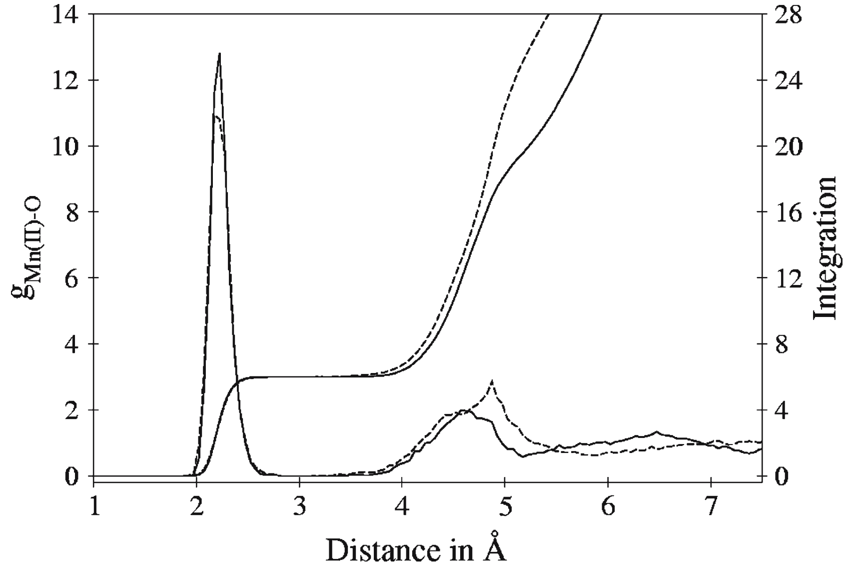

Fig. 4 Mn–O radial distribution functions and their running integration numbers for a QMCF MD (step 1, see text) (*solid line*) and a two-shell QM/MM (*dashed line*) MD simulation of Mn(II) in aqueous solution

Cu(II) is the ion, for which the largest number of experimental and simulation data are available. The data in Table 2 illustrate that inclusion of the second shell in the conventional QM/MM technique slightly shortens the distances of the nearer (i.e. "equatorial") ligands in the Jahn–Teller distorted D4h configuration. In the case of Cu(II), the possible influence of electron correlation has also been studied by means of an ab initio QM/MM MD simulation at MP/2 level [31], although only at one-shell level due to the computational effort of ~8 months. The data have shown this influence to be rather minor, and that inclusion of a second hydration shell is more important for the quality of the simulation than the inclusion of correlation effects. Application of the new formalism with fixed charge field removes the ambiguous intermediate peak between 5 and 5.5 Å (Fig. 5) – apparently a consequence of the improved smoothing for the transitions between QM and MM regions – and makes the splitting of the first shell peak due to the Jahn–Teller effect more pronounced. The average Jahn–Teller splitting of 2.0/2.3 Å for first shell ligands in the QMCF simulation corresponds very well to the EXAFS data for a dilute solution (molar Cu/water ratio 1:280), being reported as 2.04/2.29 Å [4], and the average second shell location at 4.35 Å is near to that of an EXAFS study for a five-times higher concentration (molar ratio 1:111), being 4.17 [4]. This shorter distance is connected to a reduced coordination number of ~8 in this experimental setting and can be a consequence of concentration and anion effects as well as methodical limits of the spectroscopic methods applied to the

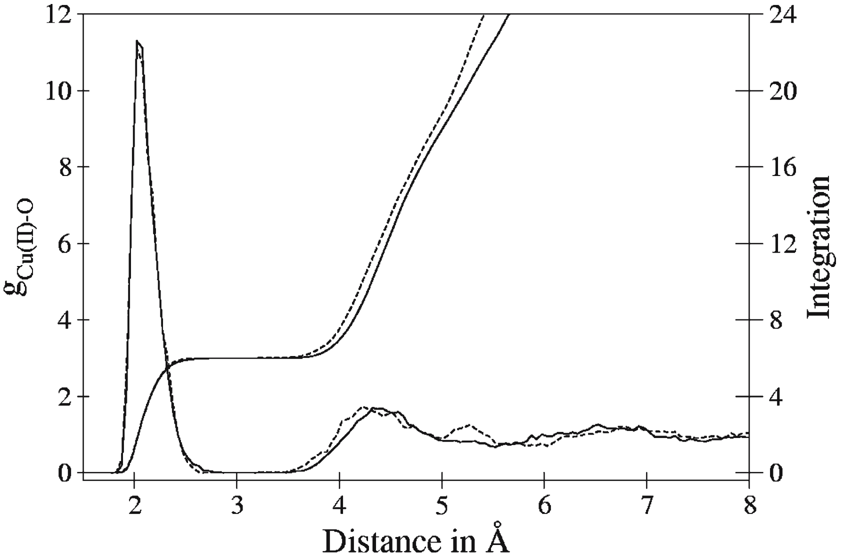

Fig. 5 Cu–O radial distribution functions and their running integration numbers for a QMCF MD (step 1, see text) (*solid line*) and a two-shell QM/MM (*dashed line*) MD simulation of Cu(II) in aqueous solution

Table 3 Maxima r_M and minima r_m of the Al(III)–O radial distribution function in Å and average coordination numbers of the respective shells

	$g_{Al(III)-O}$									
	r_{M1}	r_{m1}	r_{M2}	r_{m2}	r_{M3}	r_{m3}	$CN_{av,1}$	$CN_{av,2}$	$CN_{av,3}$	Ref.
One-shell QM/MM simulation	1.9	2.2	4.2	4.8	~6.1	7.5	6.0	13.8	42.4	[16]
Two-shell QM/MM simulation	1.8	2.1	4.1	4.7	~6.1	7.2	6.0	12.2	37.3	[16]
QMCF simulation – complete formalism	1.9	2.3	4.1	4.8	6.4	7.2	6.0	11.8	31.7	This work

Table 4 Maxima r_M and minima r_m of the Cu(II)–O radial distribution function in Å and average coordination numbers of the respective shells

	$g_{Cu(II)-O}$						
	r_{M1}	r_{m1}	r_{M2}	r_{m2}	$CN_{av,1}$	$CN_{av,2}$	Ref.
QMCF simulation – step 1	2.0	2.9	4.4	5.5	6.0	16.7	This work
QMCF simulation – complete formalism	2.03/2.25/2.35	2.9	4.5	5.3	6.0	13.5	This work

The 2nd/3rd value for r_{M1} corresponds to the slight shoulders reflecting the Jahn–Teller distortions of the first hydration shell, determined by differential analysis of the first peak

second shell with its fast dynamics ($K_{ex} = 4.4 \cdot 10^9\ s^{-1}$ [32, 33]) and wide coordination number distribution from 10 to 16 [15].

The ill-shaped second shell peaks of the Mn–O and the Cu–O radial distribution functions (RDF) seem to be a consequence of the more abrupt transition between QM and MM region in the conventional QM/MM formalism, where the subtractive method considers the same water molecules with different charges. In a one-shell simulation, this effect is partially corrected by the three-body correction function, which is not employed in two-shell simulations. In the QMCF method, however, all forces are evaluated on the basis of the quantum mechanically derived charges and, therefore, transitions between QM and MM regions are less abrupt.

Tables 3 and 4 show the comparison of characteristic results for Al(III) and Cu(II) obtained by conventional two-shell ab initio QM/MM simulations, and by the new QMCF formalism employing all of its features, that is, also the fluctuating atomic charges of the atoms within the QM region and the incorporation of the MM molecules as perturbation operator representing their atomic charges and location/orientation in the QM Hamiltonian. Figures 6 and 7 show the corresponding RDFs.

Al(III) is a test case of particular interest because of the polarisation effects expected due to the high charge of the cation. The new approach – after implementing also step 2 – is more suitable to reflect their influence, as it considers all changes in the net charges of the atoms in the course of the simulation. The results presented in Table 3 and Fig. 6 show some minor differences between the conventional two-shell QM/MM MD simulation and the QMCF test run of a few picoseconds. The peaks get slightly lower, the first peak

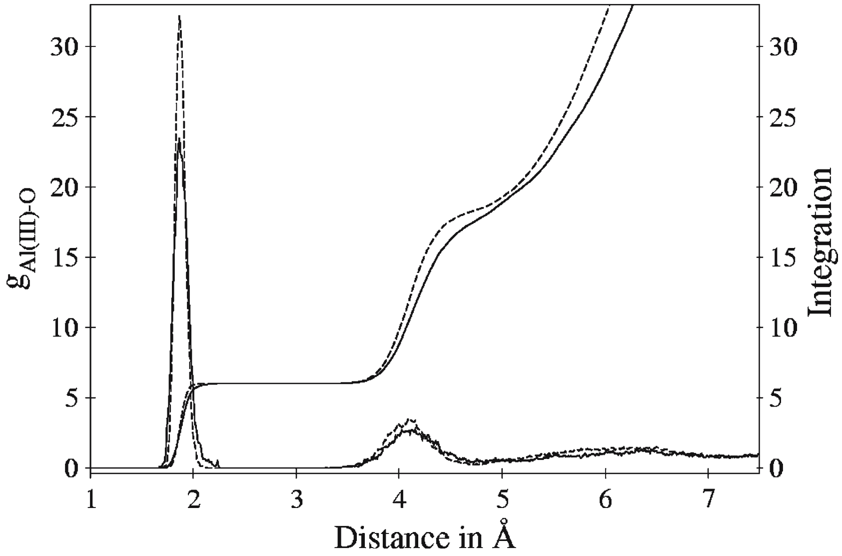

Fig. 6 Al–O radial distribution functions and their running integration numbers for a QMCF MD (complete formalism, see text) (*solid line*) and a two-shell QM/MM (*dashed line*) MD simulation of Al(III) in aqueous solution

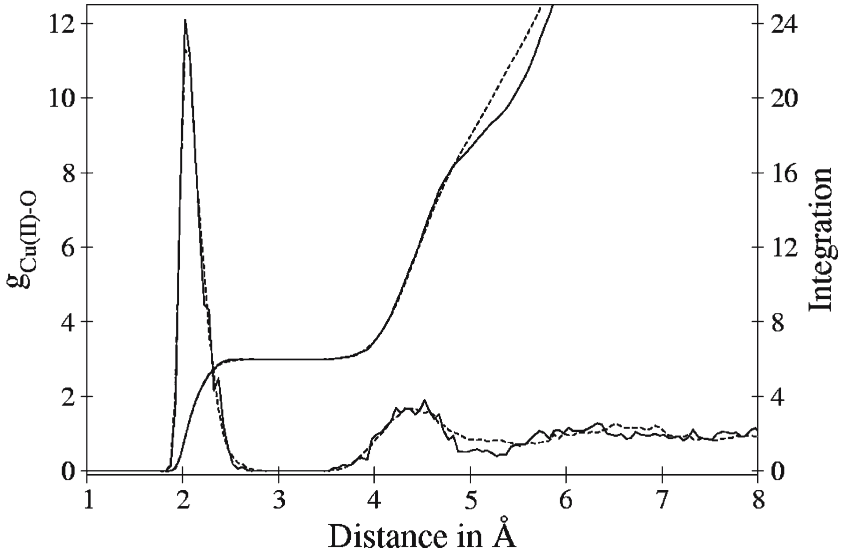

Fig. 7 Cu–O radial distribution functions and their running integration numbers for step 1 (*dashed line*) and the complete formalism (*solid line*) of a QMCF MD simulation of Cu(II) in aqueous solution

shows some tailing and a third shell can hardly be defined. It should be mentioned that in the course of the QMCF simulation some indications of a beginning dissociation of a proton from a water ligand were observed, which was never the case in the conventional simulation. The improved consideration of the fluctuating charges and the inclusion of the outer sphere charges in the Hamiltonian of the QM region can be seen as a reason for an easier occurrence of this phenomenon, which is actually known to happen in solutions of Al(III) salts, making them considerably acidic. These results show that the new formalism – which did not require the use of any Al(III)-solvent potentials – does not only produce results of equal quality as a conventional ab initio QM/MM simulation, but even can improve some of the features describing the structure of hydrated Al(III).

In the case of Cu(II) the inclusion of the charge field components leads to slight modifications compared with the formalism employing only step 1 of the QMCF method (Table 2). The explicit consideration of the fluctuating charges and the external charge field via a perturbation of the Hamiltonian apparently has only minor effects on the first shell, but the Jahn–Teller distortions become more visible. The main effect is recognised in the more compact structure of the second shell and its better separation from the bulk. Therefore, a less ambiguous determination of the average second shell hydration number has become possible, being 13.5 up to the shell border at 5.3 Å. An evaluation of further implications would have to refer to dynamical data, for which, however, a much longer simulation time would be required than the few picoseconds of the test run.

4 Conclusion

The test systems studied show clear evidence that the simulation method proposed here leads to equivalent, and even slightly improved results compared with the conventional ab initio QM/MM simulations. Improvements over the conventional method are partly due to the more continuous transition between QM and MM regions and partly a consequence of the flexible charge distribution treatment due to the continuous change of the electron distribution and its consideration in all contributions to the forces acting on the atoms/molecules in the system. The computational effort needed is almost the same as in conventional ab initio QM/MM systems and increases with the overall size of the solvate, that is, the diameter of the total QM region. The main advantage of the QM/MM-CF approach lies in its ability of a straightforward treatment of any new kind of solute without the need for evaluating individual potential functions for all interactions between the solute and solvent components by constructing ab initio energy surfaces for pair (and sometimes necessarily three-body) interactions. This gives immediate access to the study of structure and dynamics of a large number of complex species in aqueous and non-aqueous solution and to biologically active compounds in their aqueous environment. Given the continuously increasing performance of computers at decreasing cost the perspectives of the application of this method appear quite favourable.

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