JCTC Journal of Chemical Theory and Computation

Electrostatically Embedded Many-Body Expansion for Simulations

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Received August 29, 2007

Abstract: We have applied the electrostatically embedded many-body (EE-MB) method truncated at the two-body level (also called the pairwise additive EE-MB method or the EE-PA approximation) and the three-body level (called EE-3B) to calculate the gradient of the potential energy for a simulation box containing 64 water molecules. We employed the B3LYP density functional with the 6-31+G-(d,p) basis set for this test case. We found that the EE-PA method is able to reproduce the magnitude of the gradient from a B3LYP/6-31+G(d,p) calculation on the entire system to within 1.0% with a 1.3% error for the maximum component of the gradient. Furthermore, the EE-3B method is able to reproduce the magnitude of the gradient to within 0.1% with a 0.2% error for the maximum component of the gradient. The good performance of the EE-MB methods for calculating forces and the highly parallel nature of these methods make them well suited for use in molecular dynamics simulations. Furthermore, since the methods can be used for efficient and accurate calculations of forces with any level of electronic structure theory that has analytic gradients and with any electronic structure package that allows for the presence of a field of point charges, these methods can readily be used with a wide variety of density functional theory and wave function theory methods.

Molecular simulations that use molecular mechanics potentials or other analytic potentials for the potential energy surface and classical mechanics for the nuclear motion have been carried out for nearly 50 years,[1] but although molecular mechanics potentials may give good agreement with experiment for the physical properties against which they are parametrized, they often give poor results when applied to properties outside this set. As a result of this shortcoming, molecular mechanics potentials must be developed anew or revalidated for each new system of interest and even for each property one wants to study. In the interest of developing more robust methods for calculating potential energies for molecular simulations, there is great interest in the direct use of quantum mechanical methods without analytic representations, i.e., direct dynamics. In particular, a quantum mechanical theoretical model chemistry[2−4] can be validated against a broad data set for predicting potential energy surfaces or properties dependent on them; and if the validation test is sufficiently broad, the quantum mechanical model chemistry is likely to have better predictive value than molecular mechanics because it more fully incorporates the relevant physics.

Due to the large system sizes for most condensed-phase simulations, even when using periodic boundary conditions,[5,6] model chemistries based on wave function theory[3,4] (WFT) such as second-order Møller−Plesset perturbation theory (MP2),[7] coupled cluster theory with single and double excitations (CCSD),[8] or CCSD with quasiperturbative triples[9] (CCSD(T)) are currently impractical in their original formulations, in part because of the rapid scaling in cost of these methods with respect to system size. (MP2, CCSD, and CCSD(T) scale as N^5, N^6, and N^7, respectively, where N is the number of atoms in the system.[10]) As a result, most direct dynamics simulations are carried out using density functional theory[11] (DFT), whose scaling cost, with popular algorithms, increases only as N^3 or N^4. Due to the quantum mechanical nature of DFT, these simulations are significantly more expensive[12,13] than their counterparts with molecular mechanics or analytic potentials, but the added cost is rationalized in the hope that the energies obtained are much more accurate and the functionals are more transferable. A drawback to such conventional calculations is that only a relatively small number of density functionals have been implemented in the most efficient periodic-boundary-condition simulation packages, and when a newer, more accurate kind of functional becomes available, it may require specialized programming to be made available in efficient packages.

In recent years several groups have emphasized the advantage of many-body expansions[14−29] and other fragmentation methods[30−39] for calculations on large systems. A crucial aspect of using any such method for geometry optimization or for calculating forces or molecular dynamics is the ability to formulate efficient algorithms for analytic gradients of the potential energy surface. The pioneering fragment molecular orbital (FMO) method[14−18,22−24,27,28] has been particularly successful for large systems, especially proteins, and methods were developed for nearly analytic

restricted Hartree−Fock (RHF) gradients[15] and analytic derivatives of the two-body electrostatic interactions between widely separated fragments.[27] The molecular fractionation with conjugate caps method,[31−34] which does not include three-body or higher-order terms or long-range electrostatics, but rather simulates the local chemical environment of fragments with conjugate caps, has also been applied very successfully to proteins and allows[33] for convenient calculation of dimer gradients. The method has been extended to include long-range electrostatic fields both with[35] and without[36] truncation, and in the former case gradients were obtained.

We have formulated an efficient and accurate many-body expansion method in a way that yields computationally efficient energy gradients for all electronic structure levels for which they are available for the fragments,[25] and in this letter we test the accuracy of the gradients and describe the applicability to molecular simulations of this new approach, which is called the electrostatically embedded many-body (EE-MB) expansion. The EE-MB method can be used with both wave function methods such as MP2 and CCSD(T) and with DFT. For both types of methods it makes the scaling more manageable, and it has the distinct advantage that it can be used in conjunction with any electronic structure package (allowing researchers to utilize any WFT level or any density functional of their choosing). Very accurate results can be obtained in the three-body approximation[25,26,29] with a scaling of N^3. The EE-MB method is very general and can be applied to molecular liquids such as simulations of aqueous solutions or (when extended to include a scheme, such as link atoms[40−43] or conjugated caps,[32] for terminating fragments at fragment boundaries that pass through bonds) to large covalent systems such as polymers or proteins. In this work we focus on its utility for simulating molecular liquids and use pure water as an example. A key issue is that analytic gradients are available for three-body and higher-order terms as well as two-body terms and for near as well as far fragments, while retaining the key advantage that the electrostatic field of the rest of the system is not truncated.

The complete details of the EE-MB method are presented elsewhere,[25] and so here we present only a brief overview of the method. For any level of theory (e.g., MP2 or CCSD-(T) with a given basis set, or DFT with a given functional and basis) we can expand the potential energy of a system of N monomers (where a monomer can be a single molecule a small collection of molecules) in a many-body expansion given by

$$V = V_1 + V_2 + V_3 + \cdots + V_N \qquad (1)$$

where V_n is the n-body term. Truncating at V_2 is called the pairwise additive approximation (PA), and truncating at V_3 is called the three-body (3B) approximation. For a system with N monomers, V_1 involves calculating all N monomer energies, V_2 involves calculating $(N(N-1))/2$ dimer energies, and V_3 involves calculating $(N(N-1)(N-2))/3!$ trimer energies. If the n-mer calculations are performed in vacuum one has a conventional many-body expansion; however, in the EE-MB methods (where MB = PA or 3B) the n-mer calculations are performed in a field of point charges at the nuclear positions of the $N-n$ missing monomers.

The applicability of many-body expansion methods to Monte Carlo simulations has been discussed by Christie and Jordan,[21] and so in this work we will focus on application to molecular dynamics calculations. In previous work we have demonstrated the ability of the EE-MB methods to accurately reproduce the energetics of a series of water clusters ranging in size from 5 to 20 molecules.[25,26,29] In that work we found that the EE-PA method was able to reproduce the energy of a system to within 0.8% and that the EE-3B method was able to reproduce the energy to within 0.3%, and we also discussed the efficiency with which gradients could be calculated using the EE-MB method. Because the largest calculation carried out for these methods is a dimer (in the EE-PA method) or a trimer (in the EE-3B method) the problem of needing to carry out one very large calculation is reduced to carrying out a very large number of small calculations, which is more practical on most computers. In this way one also avoids the very high scaling of many WFT methods, such as CCSD(T), and this makes it possible to apply the EE-MB levels of theory to simulations of very large systems.

Within the EE-MB approximation the EE-PA and EE-3B energies can be written as

$$E_{\text{EE−PA}} = \sum_{i>j} E_{ij} - (N-2) \sum_i E_i \qquad (2)$$

$$E_{\text{EE−3B}} = \sum_{i>j>k} E_{ijk} - (N-3) \sum_{i>j} E_{ij} + \frac{(N-3)(N-2)}{2} \sum_i E_i \quad (3)$$

where N is the number of particles in the system and where E_i, E_{ij}, and E_{ijk} are the energies of the embedded monomers, dimers, and trimers. Since the gradient is a linear operator it follows that

$$\nabla E_{\text{EE−PA}} = \sum_{i<j}^N \nabla E_{ij} - (N-2) \sum_i^N \nabla E_i \qquad (4)$$

and similarly

$$\nabla E_{\text{EE−3B}} = \sum_{i>j>k} \nabla E_{ijk} - (N-3) \sum_{i>j} \nabla E_{ij} + \frac{(N-3)(N-2)}{2} \sum_i \nabla E_i \quad (5)$$

where analytic gradients are therefore available for any method that has analytic gradients for the monomer, dimer, and, in the case of the EE-3B method, trimer calculations, provided that the program allows for fractionally charged point charges as pseudonuclei. Since the magnitudes of the point charges are fixed in our EE-MB calculations, the point charges act like fractionally charged nuclei with no basis functions; therefore, as the system evolves during the course of a simulation there is no need to update the charges. Nevertheless, one should also note that all terms on the right-hand sides of eqs 4 and 5 contribute to all components of the gradient. For example, even if $m \neq i$, $m \neq j$, and $m \neq k$, one still has that ∇E_{ijk}, ∇E_{ij}, and ∇E_i all contribute to the gradient components corresponding to the coordinates of monomer m.

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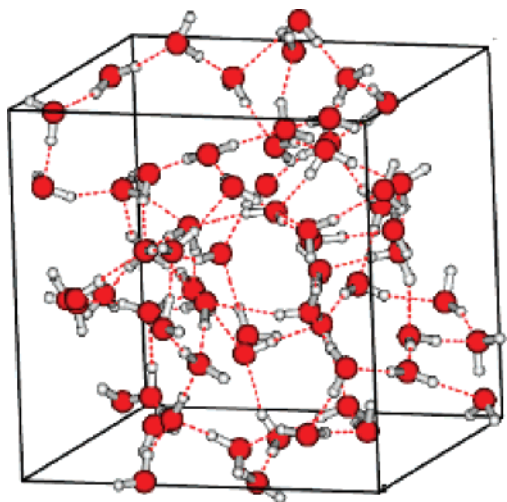*J. Chem. Theory Comput.*, Vol. 4, No. 1, 2008 **3**

Figure 1. Simulation box used for single point gradient calculation.

As mentioned previously, while the application of the EE-MB method in this work is limited to a water cluster in which there are no covalent bonds present between the monomers, the form of eq 2 is very similar to the equation used to calculate protein−ligand interactions with the molecular fractionation with conjugate caps method presented in ref 33.

In order to demonstrate the ability of the EE-MB method with fixed point charges to yield accurate gradients, we have calculated a single-point gradient on a simulation box containing 64 water molecules (see Figure 1), without periodic boundary conditions, using both the EE-PA and EE-3B methods with the B3LYP[44−47] density functional and the 6-31+G(d,p)[48] basis set, and we have compared the results to a conventional B3LYP/6-31+G(d,p) calculation on the full system. (Although the EE-MB method can be used in conjunction with WFT methods such as MP2 and CCSD-(T), we have limited ourselves for this validation test to the use of DFT because the rapid scaling of MP2 and CCSD(T) makes the calculation of a single-point gradient calculation on the full system, as required to test the EE-MB gradients, very expensive.) The work of Lenosky et al.[49] has shown that the use of a single gradient on a large system is a powerful tool for the optimization of methods, and therefore we use it here as a way to analyze the EE-MB method. Note that the gradient of a cluster of 64 water molecules provides 192 gradient components against which to test the EE-MB method.

The full calculation was carried out using the *Gaussian 03* software package.[50] The EE-PA and EE-3B calculations were carried out using the MBPAC 2007-2 software package.[51]

Table 1 compares the results of the EE-MB calculations to the gradient from the full B3LYP/6-31+G(d,p) calculation. Table 1 lists the magnitude of the gradient and the maximum component of the gradient from the EE-PA, EE-3B, and conventional B3LYP/6-31+G(d,p) calculations, the error in the gradient, the error in the maximum component of the gradient, and the mean absolute error in the components of the gradient predicted by the EE-PA and EE-3B methods. Table 1 also lists the percentage error in the magnitude of the gradient and in the maximum component of the gradient from the EE-PA, EE-3B calculations. From Table 1 it is clear that both the EE-PA and EE-3B methods are able to reproduce the forces for this system very well, with errors in the gradient of less than 0.0002 au (one atomic unit (au) of force equals one hartree per bohr) for the EE-PA method and less than 3×10^{-6} au for the EE-3B level, which corresponds to a percentage error of less than 1% for EE-PA and less than 0.01% for EE-3B. We see similarly good performance for the maximum component of the gradient, with the EE-PA method having an error of 1.3% and the EE-3B method having an error of 0.2%. The near-order-of-magnitude improvement as one goes from the EE-PA method to the EE-3B method is consistent with past studies[25,26,29] considering only energetics. The mean absolute error also shows that the EE-3B method performs better than EE-PA as it has a MAE of 4.07×10^{-4} au compared to a value of 6.23×10^{-4} au for the EE-PA method. The average magnitude of a component of the gradient is 1.37×10^{-2} au, so the mean absolute deviation as a percentage of the mean component is 4.5% for the EE-PA method and 3.0% EE-3B method.

These comparisons show that, even at the EE-PA level, the EE-MB method is able to achieve gradients in reasonable agreement with gradients calculated by conventional methods. One should be careful not to interpret the deviation as an error, just as the difference between conventional MP2 and conventional CCSD(T) is not an error but rather a difference between two model chemistries. In the present case the difference between conventional B3LYP and EE-3B/B3LYP is expected to be smaller than the difference of either from complete configuration interaction. A key issue is that eqs 4 and 5 provide an accurate theoretical model chemistry[2−4] with precise and convenient gradients. The deviation of EE-MB/DFT from conventional DFT will be of minor importance for many purposes, but the high precision of the gradients in the present algorithm will be a critical component of stable (nondrifting) molecular dynamics simulations.

Calculating the bulk properties of molecular liquids by the EE-MB method can be accomplished by employing periodic boundary conditions,[5,6] and this can be accomplished for EE-MB simulations by methods already developed for QM/MM simulations[52] augmented by a criterion to select the appropriate image of each monomer in the dimers and trimers. The latter can be accomplished by the nearest-image convention,[6] which is currently employed in simulations utilizing analytic functions for the potential energy functions. The nearest-image convention is widely used for pairwise potentials and has been modified[53] for three-body potentials, and its implementation is straightforward. Additionally, for any potential that decays more rapidly than R^{-3} (such as dispersion terms arising purely from quantum mechanical correlation) the use of a cutoff can be employed (typical cutoffs are one-half the box length for a cubic simulation box). In cases where one has long-range interactions, Ewald summations are used with molecular mechanics potentials to account for the interactions of point charges and dipolar molecules,[5] and they can be employed in the same way for the present electrostatic embedding terms.

The treatment of periodic images of the embedded quantum mechanical monomers, dimers, and trimer can be identical to methods employing periodic boundary in the context of combined quantum mechanical (QM) and mo-

Table 1. Errors in the Gradient and the Components of the Gradient (in Atomic Units) for the EE-PA and EE-3B Methods at the B3LYP/6-31+G(d,p) Level of Theory

	full	EE-PA[a]	EE-3B
magnitude of the gradient	1.8512×10^{-2}	1.8695×10^{-2}	1.8509×10^{-2}
max. component of the gradient	6.0892×10^{-2}	6.1686×10^{-2}	6.1005×10^{-2}
error			
magnitude of the gradient		1.8354×10^{-4}	-2.6305×10^{-6}
max. component of the gradient		7.9324×10^{-4}	1.1312×10^{-4}
% error			
magnitude of the gradient		0.99	−0.01
max. component of the gradient		1.30	0.19
MAE[b]		6.2257×10^{-4}	4.0667×10^{-4}

[a] The EE-MB calculations used point charges of −0.778 and 0.389 for oxygen and hydrogen atoms, respectively, as in past work.[25] [b] MAE denotes the mean absolute error (in atomic units) in the components of the gradient.

lecular mechanical (MM) calculations (QM/MM calculations[52,54−58]). The total energy for a QM/MM calculation can be written as

$$E(\text{QM/MM}) = E(\text{MM}) + E(\text{QM}) + E(\text{QM-MM}) \quad (6)$$

where $E(\text{MM})$ is the energy of the molecular mechanics system, $E(\text{QM})$ is the contribution from the quantum mechanical system, and $E(\text{QM-MM})$ is the contribution due to coupling of the MM and QM regions. For QM/MM methods that employ electronic embedding,[43,59−67] one of the terms in $E(\text{QM-MM})$ is computed along with $E(\text{QM})$ by calculating $E(\text{QM})$ in a field of molecular mechanics point charges. Therefore, each embedded monomer, dimer, or trimer calculation in an EE-MB calculation can be thought of as a simplified QM/MM calculation, in which the $E(\text{MM})$ term is zero (the interaction energy of the point charges is not included in the total EE-MB energy), and the only contribution to the $E(\text{QM-MM})$ term is from embedding the n-mer in an environment of point charges. There are a number[52,54,57,58,66,67] of examples in the literature in which periodic boundary conditions have been applied successfully to QM/MM calculations, and QM/MM codes can be used in conjunction with the EE-MB method by writing a subroutine to interface the existing code with the electronic structure package of one's choosing to carry out the EE-MB calculation. Furthermore, because all of the monomer, dimer, and trimer calculations are independent of each other, the EE-MB method is highly parallel, which allows for rapid energy calculations, even on very large systems.

Due to the expense of an accurate treatment of the electronic wave function near the nucleus of an atom, a variety of specialized approximations and procedures have been developed for plane-wave simulations of condensed-phase systems.[68−75] For example, ultrasoft pseudopotentials[68,70] are often used to keep the plane wave cutoff low, and such pseudopotentials must be carefully optimized to minimize inaccuracies.[71−73] Due to the small system sizes calculated in the EE-MB methods, all calculations can be carried out without pseudopotentials or with norm-conserving[76] (also called shape-consistent[77]) effective core potentials, which are less economical but more accurate. Also, well validated techniques developed for small-molecule calculations can be used.

It is interesting to consider the amount of time needed to carry out these kinds of calculations. Table 2 presents a series of hypothetical timings, for a calculation on 64 molecules,

Table 2. Comparison of Hypothetical Timings for Full Calculations and EE-MB Calculations for a System Containing 64 Molecules

scaling	conventional	EE-PA	EE-3B
aN^3	$2.6 \times 10^5\ a$	$1.6 \times 10^4\ a$	$3.5 \times 10^5\ a$
bN^4	$1.7 \times 10^7\ b$	$3.2 \times 10^4\ b$	$7.0 \times 10^5\ b$
cN^7	$4.4 \times 10^{12}\ c$	$2.5 \times 10^5\ c$	$5.6 \times 10^6\ c$

for methods that scale as aN^3 (e.g., BLYP, PBE, and M06-L), bN^4 (e.g., B3LYP, M06-2X), and cN^7 (e.g., MP4, CCSD-(T)), where N is the number of atoms in the system, and a, b, and c are unknown prefactors, specific to each level of electronic structure theory. (It is an approximation to assume that this scaling holds for all N, including small N, but timing analyses are inherently approximate, and the present timing discussion is intended to illustrate scaling issues—not to be quantitative.) Table 2 shows that even on a single processor, the many-body approaches are far more cost-effective than conventional calculations. In this example, use of the EE-3B method would reduce the cost of a method that scales as cN^7 by 6 orders of magnitude on a system of 64 molecules, and use of the EE-PA method would reduce the cost by 7 orders of magnitude. Even for density functional theory it is clear from Table 2 that the EE-MB methods are cost-effective. For hybrid methods, such as B3LYP or M06-2X that scale as bN^4, both the EE-PA and EE-3B methods are less expensive than a conventional calculation on the full clusters. For nonhybrid methods the EE-PA method is an order of magnitude less expensive, and the EE-3B calculation is only a factor of 1.3 more expensive.

All calculations in Table 2, both conventional and EE-MB, can be further speeded up by linear scaling algorithms,[18,52,78,79] but quantitative speedups depend strongly on the program and will not be estimated here. Nevertheless it is worthwhile to note that linear scaling can be achieved in EE-MB by using a cutoff to reduce the number of two-body or three-body terms that must be calculated. We showed that if a cutoff of 6 Å is used, then even for a cluster as small as $(H_2O)_{20}$ one can eliminate up to 44% of the pairs.[26] A key issue here is that the introduction of linear scaling is much simpler in the EE-MB approximation than in other methods of comparable accuracy because it simply involves limiting the number of dimers and/or trimers considered, but it does not require cutting off long-range electrostatics when they are treated by Ewald.

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In summary, we have found that both the EE-PA and EE-3B methods are able to reproduce the gradient and the maximum component of the gradient for a simulation box containing 64 water molecules to within 1% and 0.1% respectively, at the B3LYP/6-31+G(d,p) level of theory. Probably more important though is the high-precision attainable when EE-MB methods are used as a theoretical model chemistry. Additionally, the EE-MB methods are designed in such a way as to allow the straightforward introduction of periodic boundary conditions, so that they give a promising alternative to current simulation techniques for molecular liquids.

An important advantage of the EE-MB methods is that they can easily be employed with any electronic structure package that allows for using a field of background point charges. Furthermore once implemented for a given electronic structure package, the EE-MB program is available for all electronic structure levels available in that package. It is very efficient for any density functional or wave function theory that has analytic gradients, and it can provide a substantial savings in cost for large systems.

Supporting Information Available: Geometry and B3LYP/6-31+G(d,p) energy and gradient for the 64-molecule cluster. This material is available free of charge via the Internet at http://pubs.acs.org.

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