

Supplementary information

Polarizable embedding QM/MM: the future gold standard for complex (bio)systems?

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In this supporting information, we present with greater detail all the quantities that need to be computed for a general polarizable QM/MM implementation based on distributed multipoles and induced point dipoles. We also analyze in detail the computational cost of all the steps involved, providing its formal scaling. In section S1, the polarizable QM/MM contributions to the ground state energy are presented. In section S2, we detail the calculation of the contributions to the forces. Finally, in section S3, we present the polarizable QM/MM contributions to the gradient of the excitation energy computed using the linear response theory.

S1 General treatment of electrostatic interactions for polarizable QM/MM

Let M_i^L be a Cartesian multipole of angular momentum L placed at the i -th MM atom and let \mathbf{r}_i be the position of such an atom. For the sake of notation simplicity, the Cartesian indices of the various tensors are not reported, and implicit sums are always assumed. Also, we assume that the nuclear charges of the QM atoms are included in the electrostatic distribution (ED), as their contributions are completely equivalent to the ones of the distributed multipoles. The energy of a distribution of point multipoles can be written as

$$\mathcal{E}^{\text{ED}} = \frac{1}{2} \sum_i \sum_{L_1} \sum_{j \neq i} s_{ij} \sum_{L_2} M_i^{L_1} T_{ij}^{L_1 L_2} M_j^{L_2}, \quad (\text{S1})$$

where

$$[T_{ij}^{L_1 L_2}]_{\alpha' \beta' \dots}^{\alpha \beta \dots} = \frac{\partial^{L_1}}{\partial r_i^\alpha \partial r_i^\beta \dots} \frac{\partial^{L_2}}{\partial r_j^{\alpha'} \partial r_j^{\beta'} \dots} \frac{1}{|\mathbf{r}_i - \mathbf{r}_j|} \quad (\text{S2})$$

and s_{ij} is a scaling factor, that can be set to zero to exclude an interaction, for instance between two bonded atoms, or to an intermediate value to scale it, according with the specific force field exclusion rules. We also introduce a modified Coulomb interaction tensor that includes a damping function

$$[\mathcal{T}_{ij}^{L_1 L_2}]_{\alpha' \beta' \dots}^{\alpha \beta \dots} = \frac{\partial^{L_1}}{\partial r_i^\alpha \partial r_i^\beta \dots} \frac{\partial^{L_2}}{\partial r_j^{\alpha'} \partial r_j^{\beta'} \dots} \frac{\lambda_1(|\mathbf{r}_i - \mathbf{r}_j|)}{|\mathbf{r}_i - \mathbf{r}_j|}. \quad (\text{S3})$$

The damping function $\lambda_1(|\mathbf{r}_i - \mathbf{r}_j|)$ ensures that the coulomb interaction between two point multipoles does not diverge when the two get too close and is a fundamental ingredient of polarizable force field, as it allows them to avoid the so-called polarization catastrophe.

The first step requires assembling the ED energy. Using eq. S1, this can be achieved by first computing the potential ($L = 0$) and, if required, higher order electrostatic properties at the MM atoms (e.g., electric field, $L = 1$, field gradient, $L = 2, \dots$)

$$\Phi_i^{L_1} = (-1)^{L_1} \sum_{j \neq i} \sum_{L_2} T_{ij}^{L_1 L_2} M_j^{L_2} \quad (\text{S4})$$

and then contracting with the distributed multipoles

$$\mathcal{E}^{\text{ED}} = \frac{1}{2} \sum_i \sum_{L_1} (-1)^{L_1} M_i^{L_1} \Phi_i^{L_1}. \quad (\text{S5})$$

Eq. S4 requires in principle $\mathcal{O}(N^2)$ flops. Recently, we developed a general, linear scaling machinery that can handle all the electrostatic properties evaluations needed for energy and forces associated with a polarizable embedding scheme including distributed multipoles up to the quadrupole and induced dipoles¹. Thanks to this machinery, which is based on the Fast Multipole Method² modified to account for screened and damped interactions^{1,3}, we can evaluate eq. S4 with

$\mathcal{O}(N)$ floating point operations. We remind here that for convenience, we have included the nuclear charges of the QM atoms in the ED, so the electrostatic energy contains the nuclear repulsion energy as well.

The second step requires another evaluation of eq. S4, this time with $L = 1$, but with the damped Coulomb kernel:

$$E_i^{\text{MM}} = - \sum_{j \neq i} \sum_{L_2} s_{ij} \mathcal{F}_{ij}^{L_2} M_j^{L_2}. \quad (\text{S6})$$

Again, this can be achieved with linear-scaling computational cost using the FMM. We note here that if the AMOEBA force field is used, two different inducing fields need to be assembled, each computed with different exclusion rules (i.e., scaling factors s_{ij}). We refer to previous work for more details⁴⁻⁷.

The third step requires the evaluation of one-electron potential integrals and, possibly, integral derivatives. By introducing the operator

$$\hat{T}_i^L(\mathbf{r}) = \frac{\partial^L}{\partial r_i^\alpha \partial r_i^\beta \dots} \frac{1}{|\mathbf{r} - \mathbf{r}_i|}, \quad (\text{S7})$$

the one-electron Hamiltonian contributions stemming from the ED can be written as

$$V_{\mu\nu}^{\text{ED}} = \sum_i \sum_L M_i^L \langle \chi_\mu(\mathbf{r}) | \hat{T}_i^L(\mathbf{r}) | \chi_\nu(\mathbf{r}) \rangle, \quad (\text{S8})$$

where χ_μ, χ_ν are atomic orbitals (AO) basis functions. The integrals in eq. S8 are standard and available in most QM codes. The overall cost of evaluating eq. S8 is proportional to the product of the number of QM (N_{QM}) and MM atoms (N_{MM}), and therefore still linear in the number of MM atoms. Assuming, as it is reasonable, that the number of QM atoms is much smaller than the number of MM atoms, the evaluation of the one-electron Hamiltonian contributions is overall mostly inexpensive.

The following steps are to be repeated at each SCF iteration. Given the current density matrix $P_{\mu\nu}$, one first need to assemble the QM electric field at the polarizable sites:

$$E_i^{\text{QM}} = - \sum_{\mu\nu} P_{\mu\nu} \langle \chi_\mu(\mathbf{r}) | \hat{T}_i^1(\mathbf{r}) | \chi_\nu(\mathbf{r}) \rangle \quad (\text{S9})$$

Again, eq. S9 can be evaluated using standard one-electron integrals, for a computational cost scaling as $\mathcal{O}(N_{\text{MM}}N_{\text{QM}})$. At this point, the IPD are computed by solving the polarization equations

$$\alpha_i^{-1} \mu_i + \sum_{j \neq i} s_{ij} \mathcal{F}_{ij}^{11} \mu_j = E_i^{\text{MM}} + E_i^{\text{QM}}, \quad (\text{S10})$$

where α_i is the isotropic polarizability of the i -th polarizable site. The linear system in eq. S10 is symmetric and positive definite and can therefore be solved iteratively using the preconditioned conjugate gradient (PCG) method⁶. To accelerate convergence, we employ the preconditioner suggested by Wang and Skeel⁸, thanks to which tight convergence (10^{-8} root mean square norm of the residual) can be achieved in about 10-12 iterations. Solving the polarization linear system is by far the most expensive task associated with a polarizable embedding scheme. However, the matrix-vector product in eq. S10 can be assembled at $\mathcal{O}(N_{\text{MM}})$ cost using the FMM with the appropriate modifications, as described in detail in references 3 and 1. Thanks to our linear scaling implementation, this step can be performed with limited computational cost even for the largest embeddings. Once the polarization equations have been solved, the polarization energy is assembled as

$$\mathcal{E}^{\text{pol}} = - \frac{1}{2} \sum_i \mu_i (E_i^{\text{MM}} + E_i^{\text{QM}}). \quad (\text{S11})$$

Finally, the PE contributions to the Fock (KS) matrix are given by

$$V_{\mu\nu}^{\text{pol}} = - \sum_i \mu_i \langle \chi_\mu(\mathbf{r}) | \hat{T}_i^1(\mathbf{r}) | \chi_\nu(\mathbf{r}) \rangle. \quad (\text{S12})$$

Again, eq. S12 involves standard integrals and can be assembled at $\mathcal{O}(N_{\text{MM}}N_{\text{QM}})$ cost. To recapitulate, at each SCF cycle one needs to assemble the QM field, which requires $\mathcal{O}(N_{\text{MM}}N_{\text{QM}})$ flops, solve the polarization equations - $\mathcal{O}(N_{\text{MM}})$ flops

- and assemble the PE Fock matrix contributions - $\mathcal{O}(N_{\text{MM}}N_{\text{QM}})$. We note that, in our implementation, the overhead due to the presence of a polarizable embedding is overall scaling linearly in computational cost with respect to the number of MM atoms, which allows one to apply a PE description to very large systems without introducing major computational bottlenecks. We also note here that if the AMOEBA force field is used for the embedding, two sets of induced dipoles need to be considered^{7,9}. This doubles the computational cost of solving the polarization equations, but can nevertheless be easily done even for very large systems¹.

S2 Analytical gradients of the ground state energy

After the energy has been computed, the computation of the forces requires three additional steps. The first contribution stems from the gradients of the QM/MM interaction energy and is obtained by straightforward differentiation:

$$F_i^{\text{QM/MM}} = -\nabla_i \sum_k \sum_L M_k^L \sum_{\mu\nu} P_{\mu\nu} \langle \chi_\mu(\mathbf{r}) | \hat{T}_k^L(\mathbf{r}) | \chi_\nu(\mathbf{r}) \rangle. \quad (\text{S13})$$

Depending on whether the index i refers to a QM or to a MM atom, one needs to evaluate electrostatic properties integrals with differentiated basis functions or just higher order electrostatic properties integrals, respectively, and then contract them with the density matrix and the multipoles. Both operations are achieved using standard one-electron integrals, with a $\mathcal{O}(N_{\text{MM}}N_{\text{QM}})$ computational cost. Note that there is no need to distinguish between the distributed multipoles of the ED and the induced dipoles, that can be just added together before evaluating eq. S13. Note that if the distributed multipoles include terms higher than point charge, there is a further contribution that needs to be assembled. Distributed multipoles are in fact given in a molecular frame and need to be rotated to the lab frame. The rotation matrices depend on the coordinates and therefore give a contribution to the gradients. This contribution is very cumbersome, but straightforward and will not be discussed here. The reader can refer to previous work^{5,6} for all details. Note that these contributions, usually referred to as torques, can also be evaluated at a cost that scales linearly with the size of the MM subsystem.

The purely classical contributions to the forces are obtained by differentiating eq. S1 and eq. S11. Starting with the ED, one gets

$$F_i^{\text{ED}} = \sum_{L_1} \sum_{j \neq i} s_{ij} \sum_{L_2} M_i^{L_1} T_{ij}^{L_1+1L_2} M_j^{L_2}, \quad (\text{S14})$$

that is, the forces can be assembling by first evaluating

$$\Phi_i^{L_1+1} = (-1)^{L_1+1} \sum_{j \neq i} \sum_{L_2} T_{ij}^{L_1+1L_2} M_j^{L_2} \quad (\text{S15})$$

and then contracting with the distributed multipoles

$$F_i^{\text{ED}} = \sum_{L_1} (-1)^{L_1} M_i^{L_1} \Phi_i^{L_1}. \quad (\text{S16})$$

The evaluation of eq. S15 can be performed using the same linear scaling machinery used for the energy, and thus at $\mathcal{O}(N_{\text{MM}})$ computational cost. A torque term also needs to be evaluate for this contribution if distributed multipoles of higher order than point charges are included.

Finally, the polarization forces are obtained by differentiating eq. S11. As already mentioned, the terms stemming from the interaction of the induced dipoles with the QM field can be computed together with the other QM/MM forces, as in eq. S13. We will therefore focus on the purely classical contributions. We get

$$F_i^{\text{Pol}} = -\mu_i \sum_j \mathcal{F}_{ij}^{21} \mu_j + \mu_i \sum_{j \neq i} \sum_{L_2} s_{ij} \mathcal{F}_{ij}^{2L_2} M_j^{L_2} + \sum_L M_i^L \sum_{j \neq i} \mathcal{F}_{ij}^{L+1,1} \mu_j. \quad (\text{S17})$$

All the terms in eq. S17 can be written as the contraction of either the distributed multipoles or the induced dipoles with the appropriate electrostatic property. Once again, thanks to our general linear-scaling machinery, all this terms can be assembled with a $\mathcal{O}(N_{\text{MM}})$ computational cost. A third torque-like contribution needs to be evaluated here as well if the distributed multipoles include terms of higher order than point charges.

S3 Gradients of the linear response excitation energy

The ingredients for performing excited state MD simulations are the energy and gradients of the state of interest. In this discussion we assume the excited states are described within a linear response formalism (TD-HF, TD-DFT or CIS). The required QM/MM steps build on top of the ones presented in the previous section, according to the following scheme.

1. At each iteration of the linear response equations
 - Compute the electric field of the transition density at the polarizable sites
 - Solve the polarization equations and compute the polarization energy
 - Add the polarization contributions to the Fock (Kohn-Sham, KS) Matrix
2. Solve the Z-vector equations
3. Compute the linear response contribution to the forces
4. Compute the relaxation contribution to the forces

In a linear response scheme, the transition density and excitation energies are found as eigenvectors and eigenvalues of the molecular Hessian by solving the so called Casida's equations. Usually, the problem is solved using an iterative method which requires doing matrix–vector products between the molecular Hessian and the transition density at the current iteration. So at each step, given the guess for the transition density P^{tr} , the transition field is assembled and the polarization equations are solved

$$E_i^{\text{tr}} = - \sum_{\mu\nu} P_{\mu\nu}^{\text{tr}} \langle \chi_\mu | \hat{T}_i^1 | \chi_\nu \rangle \quad (\text{S18})$$

$$\alpha_i^{-1} \mu_i^{\text{tr}} + \sum_{j \neq i} s_{ij} \mathcal{T}_{ij}^{11} \mu_j^{\text{tr}} = E_i^{\text{tr}}. \quad (\text{S19})$$

Afterwards, the polarization contribution to the matrix–vector product is computed

$$\mathcal{V}_{\mu\nu} = - \sum_i \mu_i^{\text{tr}} \langle \chi_\mu(\mathbf{r}) | \hat{T}_i^1(\mathbf{r}) | \chi_\nu(\mathbf{r}) \rangle. \quad (\text{S20})$$

Forces are computed as analytical gradients of the TD energy Lagrangian proposed by Furche¹⁰, which we recall is variational in the MO coefficients and simplifies the derivatives. However, building the Lagrangian requires solving another set of equations, the so called Z-vector equations¹¹. Taking the gradient of the Lagrangian leads to two kinds of contributions. The first is the gradient of eq. S20 contracted with the transition density

$$F_i^{\text{tr}} = - \nabla_i \sum_j \sum_{\mu\nu} P_{\mu\nu}^{\text{tr}} \mu_j^{\text{tr}} \langle \chi_\mu(\mathbf{r}) | \hat{T}_i^1(\mathbf{r}) | \chi_\nu(\mathbf{r}) \rangle. \quad (\text{S21})$$

The second is related to the electron density relaxation, and it is computed similarly to ground state QM/MM forces (eq. S13) with the relaxed difference density (P^Δ) in place of the SCF density

$$F_i^\Delta = - \nabla_i \sum_k \sum_L M_k^L \sum_{\mu\nu} P_{\mu\nu}^\Delta \langle \chi_\mu(\mathbf{r}) | \hat{T}_k^L(\mathbf{r}) | \chi_\nu(\mathbf{r}) \rangle. \quad (\text{S22})$$

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