Computation of Forces arising from the Polarizable Continuum Model within the Domain-Decomposition Paradigm

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Within implicit solvation models, the domain-decomposition strategy for the computation of the electrostatic energy due to the solvent based on the Polarizable Continuum Model (PCM) has recently been developed. The methodological development started with the so-called ddCOSMO method and has recently be generalized to the PCM equation resulting in the ddPCM-method [Stamm *et al.*, J. Chem. Phys. 144, 054101 (2016)] for which derive the forces within this article. We show the derivation of the forces and derive an efficient implementation followed by numerical tests.

I. INTRODUCTION

Solvation-effects play a crucial role in many processes in chemistry and bio-chemistry. The individual solvent molecules in a solute-solvent system can not always been taken explicitly into account, in particular if a quantum-mechanical description of the molecular system is considered. On the other hand, solvation-effects can not be neglected. A compromise is therefore to have a limited description of the solvent, as the solvent *per se* is not of interest, but rather its effect on the solute molecule.

Polarizable continuum solvation models (PCSM)[1–18] focuses on the electrostatic interaction between the solute and the solvent which replaces the solvent by an infinite continuum with dielectric permittivity of the bulk-solvent. Such a compromise turns out to be a good balance between accuracy and cost to compute electric, magnetic, vibrational and mixed properties[1,5,19]. As a result, PCSM are nowadays available in most quantum chemistry codes and have become a standard tool, which can be successfully used by an extended community.

In standard implementations, which are usually based on the Boundary Element Method[1,20–24] (BEM), PCSM require one to numerically solve a discretized integral equation, which in practical terms requires the solution of a linear system the size of which scales linearly, but with a large constant (a rough estimate would be 50–100), with respect to the number of atoms. This is usually done using dense linear algebra techniques, such as LU decomposition[25], which require a computational effort proportional to the cube of the size of the linear system: such an operation can therefore rapidly become demanding when dealing with systems as large as the ones treated via QM/MM methods: other strategies become mandatory. Iterative techniques can be used to reduce the computational cost to the cost of several matrix-vector multiplications[26], avoiding thus cubic operations; fast summation techniques, typically, the Fast Multipole Method (FMM)[27], can then be used to further reduce the cost of solving the PCSM linear equations to a number of floating point operations which is linear in the number of atoms. Nevertheless, the solution of the PCSM equations can still represent a formidable bottleneck for large systems[28], especially, when repeated computations are required for statistical sampling purposes or time-dependent simulations.

In recent years, domain-decomposition approaches have been proposed by some of us for

PCSM. A completely different strategy[29] to solve the PCSM equation for the Conductor-like Screening Model[8] (COSMO) in combination with Van der Waals molecular cavities has been introduced, referred to as ddCOSMO[28–31]. The COSMO equation, in its differential form, is rewritten as a system of coupled linear differential equations, one per sphere, where only overlapping spheres are actually coupled. The differential equations on each sphere can then be recast as integral equations and solved very efficiently by using a (truncated) expansion in spherical harmonics[29]. The discretization produces a block-sparse linear system[30], where only the blocks corresponding to overlapping spheres are non-zero: this structure allows for a computational cost that scales linearly with respect to the number of atoms and is overall very small as compared to previous implementations: as far as two or three orders of magnitude are gained, as shown in a recent publication[28].

Recently, the method has been generalized to the PCM-equations, thus assuming a finite permittivity of the solvent, which resulted in the ddPCM-method[32] that is based on the same domain-decomposition approach. While the method has been developed in[32] to compute the electrostatic contribution to the solvation energy, the aim of this article is to present the derivation of analytical forces of the ddPCM-solvation energy.

This paper is organized as follows. Section II reviews the ddPCM and ddCOSMO methods that we have previously developed. In Section III we describe the derivation of the ddPCM forces and discuss their efficient implementation. Section IV is devoted to numerical experiments. Finally, in Section V we draw conclusions from the presented work and point to possible future directions of research.

II. A BRIEF REVIEW OF THE DDPCM STRATEGY

The foundation of Polarizable Continuum Solvation Models (PCSM's) is the assumption that the solvent in a solute-solvent system can be treated as either a dielectric, or a conducting continuum medium on the outside of the molecular cavity Ω of the solute. We follow the customary approach of taking the cavity to be the so-called Van der Waals cavity[1], i.e., the union of spheres centered at each atom with radii coinciding with the van der Waals radii. Within this approach, the topologically similar Solvent Accessible Surface (SAS) cavity can be treated as well. Models based on the Solvent Excluded Surface (SES) have also been proposed[33–36], but will not be considered here.

The electrostatic part of the solute-solvent interaction is given by $E_s = \frac{1}{2}\, f(\varepsilon) \int_\Omega \rho(x) W(x)\, dx$, where $f(\varepsilon)$ is an empirical scaling that depends on the dielectric constant of the solvent (and which is only applied in the case of the COSMO), ρ is the charge density of the solute, and W is the polarization potential of the solvent. The quantities W and E_s are usually referred to, respectively, as the reaction potential and the electrostatic contribution to the solvation energy.

The reaction potential is defined as $W = \varphi - \Phi$, where φ is the total electrostatic potential of the solute-solvent system and Φ is the potential of the solute *in vacuo*. In the case of the PCM, the total potential φ satisfies a (generalized) Poisson equation with suitable interface conditions[11,12]. Indeed, if ε_s is the macroscopic, zero-frequency relative dielectric permittivity of the solvent, and define $\varepsilon(x) = 1$ when $x \in \Omega$ and $\varepsilon(x) = \varepsilon_s$ otherwise, the reaction potential fulfills

$$\begin{cases} \Delta W = 0 & \text{in } \mathbb{R}^3 \setminus \Gamma \\ [W] = 0 & \text{on } \Gamma \\ [\varepsilon\, \partial_\nu W] = (\varepsilon_s - 1)\partial_\nu \Phi & \text{on } \Gamma \end{cases} \tag{1}$$

Here $\Gamma = \partial\Omega$ is the boundary of the cavity, ∂_ν is the normal derivative on Γ, and $[\,\cdot\,]$ is the jump operator (inside minus outside) on Γ.

Recalling potential theory, W can be represented as $W(x) = (\tilde{\mathcal{S}}\sigma)(x)$ when $x \in \mathbb{R}^3 \setminus \Gamma$, or $W(s) = (\mathcal{S}\sigma)(s)$ when $s \in \Gamma$. The surface density σ defined on Γ is the so-called apparent surface charge, $\tilde{\mathcal{S}}$ is the single layer potential and $\mathcal{S}$ is the single layer operator, which is invertible[37]. Note that both $\tilde{\mathcal{S}}$ and $\mathcal{S}$ are based on the surface Γ. It can be shown that σ satisfies the equation $\sigma = 1/4\pi\, [\partial_\nu W]$, so that it is possible to recast the PCM problem (1) as a single integral equation for σ. In fact, if we define the operators

$$\mathcal{R}_\varepsilon = 2\pi \frac{\varepsilon + 1}{\varepsilon - 1} \mathcal{I} - \mathcal{D} \qquad , \qquad \mathcal{R}_\infty = 2\pi \mathcal{I} - \mathcal{D} \tag{2}$$

where $\mathcal{I}$ is the identity and $\mathcal{D}$ is the double layer boundary operator (also based on Γ). It can be shown[1] that the apparent surface charge satisfies

$$\mathcal{R}_\varepsilon\, \mathcal{S}\, \sigma = -\mathcal{R}_\infty\, \Phi \qquad \text{on } \Gamma \tag{3}$$

which is known as the IEF-PCM equation. It involves operators $\mathcal{R}_\infty$ and $\mathcal{R}_\varepsilon$, which are both invertible. Furthermore, when the dielectric constant ε_s approaches infinity, the IEF-PCM equation simplifies to $\mathcal{S}\,\sigma = -\Phi$ on Γ, which is the Integral Equation Formulation of the Conductor-like Screening Model (COSMO)[16].

Let us recall how to solve equation (3) within the domain-decomposition paradigm. The first step is to write the IEF-PCM integral equation (3) as a succession of two integral equations, one of which is equivalent to the COSMO equation[38]. Indeed, if we define $\Phi_\varepsilon = \mathcal{S}\,\sigma$, equation (3) becomes

$$\mathcal{R}_\varepsilon\,\Phi_\varepsilon = \mathcal{R}_\infty\,\Phi \qquad \text{on } \Gamma \tag{4}$$

$$\mathcal{S}\,\sigma = -\Phi_\varepsilon \qquad \text{on } \Gamma \tag{5}$$

The ddPCM strategy is an extension of ddCOSMO in the following sense: first, equation (4) is solved in order to compute the right-hand side $-\Phi_\varepsilon$ of equation (5); secondly, ddCOSMO is employed to solve equation (5) with the modified potential $-\Phi_\varepsilon$, and compute the solvation energy E_s.

In order to discuss the domain-decomposition approach employed for both steps, let us introduce some notation. As anticipated, we take the cavity Ω be the union of M spheres $\Omega_j = B(x_j, r_j)$ with boundaries Γ_j. Let $U_j : \Gamma_j \to \mathbb{R}$ be the characteristic function of $\Gamma_j^{\mathrm{ext}} := \Gamma_j \cap \Gamma$, and define extensions $\Phi_j, \Phi_{\varepsilon,j} : \Gamma_j \to \mathbb{R}$ as $\Phi_j(s) = U_j(s)\,\widetilde{\Phi}(s)$ and $\Phi_{\varepsilon,j}(s) = U_j(s)\,\widetilde{\Phi}_\varepsilon(s)$ for $s \in \Gamma_j$, where $\tilde{(\cdot)}$ indicates the trivial extension to $\overline{\Omega}$.

Step 1. We enforce the integral equation (4) on Γ_j^{ext}, along with the boundary condition $\Phi_{\varepsilon,j} = 0$ on Γ_j^{int}, by the single local integral equation

$$\alpha(1 - U_j)\,\Phi_{\varepsilon,j} + U_j\,\mathcal{R}_\varepsilon\,\Phi_\varepsilon = U_j\,\mathcal{R}_\infty\,\Phi \qquad \text{on } \Gamma_j \tag{6}$$

where α is an arbitrary nonzero scalar, and $\mathcal{R}_\varepsilon\,\Phi_\varepsilon$ and $\mathcal{R}_\infty\,\Phi$ should be understood as their trivial extensions to Γ_j. Employing the extensions $\Phi_j, \Phi_{\varepsilon,j}$, the double layer operator $\mathcal{D}$ can be decomposed as

$$(\mathcal{D}\,\Phi)(s) = (\mathcal{D}_j\,\Phi_j)(s) + \sum_{k \neq j} (\tilde{\mathcal{D}}_k\,\Phi_k)(s) \qquad ; \qquad s \in \Gamma_j^{\mathrm{ext}} \quad , \quad j = 1, \ldots, M$$

where $\mathcal{D}_j$ and $\tilde{\mathcal{D}}_j$ are, respectively, the local double layer operator and the local double layer potential on Γ_j. We refer to[32] for concise details for these operators. Thus, we can also decompose $\mathcal{R}_\varepsilon$ in (6) as

$$(\mathcal{R}_\varepsilon\,\Phi_\varepsilon)(s) = (\mathcal{R}_{\varepsilon,j}\,\Phi_{\varepsilon,j})(s) + \sum_{k \neq j} (\tilde{\mathcal{R}}_{\varepsilon,k}\,\Phi_{\varepsilon,k})(s) \qquad ; \qquad s \in \Gamma_j^{\mathrm{ext}} \quad , \quad j = 1, \ldots, M \tag{7}$$

where the local operators $\mathcal{R}_{\varepsilon,j}$ and $\tilde{\mathcal{R}}_{\varepsilon,j}$ are defined as

$$\mathcal{R}_{\varepsilon,j} = 2\pi\frac{\varepsilon+1}{\varepsilon-1}\mathcal{I} - \mathcal{D}_j \qquad , \qquad \tilde{\mathcal{R}}_{\varepsilon,j} = -\tilde{\mathcal{D}}_j$$

with the obvious extension to the case $\varepsilon = \infty$. If we insert (7) into (6) and select $\alpha = 2\pi(\varepsilon+1)/(\varepsilon-1)$, we obtain a convenient form in terms of the local double layer potentials and double layer operators:

$$2\pi\,\frac{\varepsilon+1}{\varepsilon-1}\,\Phi_{\varepsilon,j} - U_j\left(\mathcal{D}_j\Phi_{\varepsilon,j} + \sum_{k\neq j}\tilde{\mathcal{D}}_k\,\Phi_{\varepsilon,k}\right) =$$
$$2\pi\,U_j\Phi_j - U_j\left(\mathcal{D}_j\Phi_j + \sum_{k\neq j}\tilde{\mathcal{D}}_k\,\Phi_k\right) \qquad \text{on } \Gamma_j \quad (8)$$

This constitutes our domain-decomposition strategy for equation (4). It is important to remark that, because of the summation, every subdomain Ω_j interacts with all other subdomains. We anticipate that this contrasts with the ddCOSMO strategy for equation (5).

Step 2. The restriction $W_j := W|_{\overline{\Omega}_j}$ is harmonic over the subdomain Ω_j, thus it can be represented as

$$W_j(x) = (\tilde{\mathcal{S}}_j\,\sigma_j)(x) \quad , \quad x\in\Omega_j \qquad ; \qquad W_j(s) = (\mathcal{S}_j\,\sigma_j)(s) \quad , \quad s\in\Gamma_j \qquad (9)$$

where σ_j is an unknown surface charge, and $\mathcal{S}_j$ and $\tilde{\mathcal{S}}_j$ are, respectively, the single layer potential and the single layer operator on Γ_j. The local problems (9), are coupled together by decomposing W_j as

$$W_j(s) = -U_j(s)\,\Phi_{\varepsilon,j}(s) + \big(1-U_j(s)\big)\,n_j(s)\sum_{k\in N_j}W_k(s) \qquad s\in\Gamma_j \qquad (10)$$

(replace by following, since characteristic functions are redundant)

$$W_j(s) = -\Phi_{\varepsilon,j}(s) + n_j(s)\sum_{k\in N_j}W_k(s) \qquad ; \qquad s\in\Gamma_j \quad , \quad j=1,\ldots,M \qquad (11)$$

where N_j is the set of all neighboring subdomains of Ω_j, W_k is understood as its trivial extension to Ω, and n_j is a normalization factor. If s does not belong to any neighbor of Ω_j, then $n_j(s)$ vanishes. Otherwise, $n_j(s)$ is the reciprocal of the number of neighbors. When we substitute the local problems (9) into the decomposition (10), and define $(\tilde{\mathcal{S}}_{jk}\,\sigma_k)(s) = n_j(s)\,(\tilde{\mathcal{S}}_k\,\sigma_k)(s)$, we obtain

$$\mathcal{S}_j\,\sigma_j = -U_j\,\Phi_{\varepsilon,j} + \big(1-U_j(s)\big)\sum_{k\in N_j}\tilde{\mathcal{S}}_{jk}\,\sigma_k \qquad \text{on } \Gamma_j \qquad (12)$$

(replace by following, since characteristic functions are redundant)

$$\mathcal{S}_j\,\sigma_j = -\Phi_{\varepsilon,j} + \sum_{k\in N_j} \tilde{\mathcal{S}}_{jk}\,\sigma_k \qquad \text{on } \Gamma_j \tag{13}$$

As opposed to the local problem (8) which features a global interaction of all subdomains, the ddCOSMO step (13) is characterized by the interaction of subdomain Ω_j with only its neighbors. This results in a sparse, rather than dense, discrete operator.

We discretize equation (8) and (13) by expanding Φ_j, $\Phi_{\varepsilon,j}$ and σ_j as truncated series of spherical harmonics. If Y_ℓ^m indicates the spherical harmonic of degree ℓ and order m on the unit sphere $\mathbb{S}$, we approximate the surface charge σ_j as

$$\sigma_j(s) = \sigma_j(x_j + r_j y) = \frac{1}{r_j}\sum_{\ell=0}^{L_{\max}}\sum_{m=-\ell}^{\ell}[X_j]_\ell^m\,Y_\ell^m(y)$$

for some unknown coefficients $X = [X_j]_\ell^m$ and a prescribed integer parameter $L_{\max}$. Here y is the variable on $\mathbb{S}$. We approximate $\Phi_{\varepsilon,j}$ and Φ_j in the same fashion, namely

$$\Phi_{\varepsilon,j} = -\sum_{\ell=0}^{L_{\max}}\sum_{m=-\ell}^{\ell}[G_j]_\ell^m\,Y_\ell^m \qquad , \qquad \Phi_j = -\sum_{\ell=0}^{L_{\max}}\sum_{m=-\ell}^{\ell}[F_j]_\ell^m\,Y_\ell^m$$

where $G = [G_j]_\ell^m$ and $F = [F_j]_\ell^m$ are the coefficients of the expansions, and the minus signs have been introduced for convenience. In the following, we shall use the condensed notation $\sum_{\ell,m}$ to indicate the double sum. We interpret each local problem (8) and (13) in a variational setting that uses spherical harmonics as test functions, see Appendix A. We employ orthogonality conditions of the spherical harmonics, along with Lebedev grids to perform numerical quadrature to derive discretizations of the global problems (4) and (5). Respectively, we obtain

$$A_\varepsilon\,G = A_\infty\,F \qquad , \qquad L\,X = G \tag{14}$$

and the expressions for the entries of the discrete operator A_ε are given in (A2) and (A3).

III. COMPUTATION OF THE DDPCM-FORCES

The solvation energy can be written as a sum of subdomain contributions, which perfectly fits the domain-decomposition paradigm.

First, for a classical solute's charge distribution of the form of $\rho = \sum_j q_j \delta_{x_j}$, we can develop

$$E_s = \frac{1}{2} \int_\Omega \rho(x) W(x)\, dx = \frac{1}{2} \sum_j q_j W(x_j) = 2\pi \sum_j q_j [X_j]_0^0 Y_0^0 = \sqrt{\pi} \sum_j q_j [X_j]_0^0$$

This concept easily generalizes to point multipolar charge distributions. The evaluation of the energy for charge distributions is a bit more involved as it requires a three-dimensional integration and we refer to[31] for more details. In all cases however, the energy can be written as

$$E_s = \tfrac{1}{2} \sum_j \sum_{\ell,m} [\Psi_j]_\ell^m [X_j]_\ell^m =: \tfrac{1}{2} \langle \Psi, X \rangle$$

where the angular brackets indicate the double scalar product over j and ℓ, m. For example, for the classical charge as illustrated above, we have

$$[\Psi_j]_\ell^m = \sqrt{\pi}\, q_j\, \delta_{\ell,0} \delta_{m,0}.$$

The force acting on the i-th particle can be computed as

$$\mathcal{F}_i = -\nabla_i E_s = -\tfrac{1}{2} \langle \Psi, \nabla_i X \rangle$$

where the gradient ∇_i is understood with respect to x_i and X denotes the solution to the ddPCM-equations (14). Here we used the fact that the entries of the vector Ψ are independent of the atomic positions. On the other hand, since both the matrices A_ε, A_∞ and the right-hand side F depend on the nuclear positions $x_1, \ldots, x_M$, so does the unknown X of (14), which can compactly be written as $A_\varepsilon\, L\, X = A_\infty\, F$. The idea adjoint differentiation is to consider the adjoint problem $(A_\varepsilon\, L)^* s = \Psi$ and compute the quantity $\langle \Psi, \nabla_i X \rangle = \langle s, A_\varepsilon\, L\, \nabla_i X \rangle$ by using the definition of the adjoint matrix.

If combine equations (14), the fully discretized problem becomes $A_\varepsilon\, L\, X = A_\infty\, F$, and Leibnitz differentiation rule allows to move derivatives from X onto the other terms, namely

$$A_\varepsilon\, L\, \nabla_i X = \nabla_i A_\infty\, F + A_\infty\, \nabla_i F - \nabla_i A_\varepsilon\, L\, X - A_\varepsilon\, \nabla_i L\, X =: h_i$$

Thus, once the solution s of the adjoint problem and vector h have been determined, the forces can be computed as

$$\mathcal{F}_i = -\tfrac{1}{2} \langle s, h_i \rangle$$

The derivatives $\nabla_i L$ of the ddCOSMO discretization were discussed in[30] and we now focus on the new parts due to the ddPCM-method. The quantity $\nabla_i F$ is *a priori* nonzero since

F_j is the discretization of $\Phi_j = U_j\,\tilde{\Phi}$. Wouldn't it be simple to put the formula at the end of this section?

In the remainder of this section we discuss the derivatives of the ddPCM matrix A_ε. Let $\{s_n\}$ be the N_{grid} Lebedev integration points and define the following quantities

$$t_n^{jk} = \frac{|x_j + r_j s_n - x_k|}{r_k} \quad , \quad s_n^{jk} = \frac{x_j + r_j s_n - x_k}{|x_j + r_j s_n - x_k|} \quad , \quad U_j^n = U_j(x_j + r_j s_n)$$

The blocks A_{jk}^ε of the ddPCM matrix A_ε, see (A2) and (A3), have the form

$$\begin{aligned}
[A_{jj}^\varepsilon]_{\ell\ell'}^{mm'} &= 2\pi\,\frac{\varepsilon+1}{\varepsilon-1}\,\delta_{\ell\ell'}\delta_{mm'} + \frac{2\pi}{2\ell'+1}\sum_{n=1}^{N_{\mathrm{grid}}} w_n\,U_j^n\,Y_\ell^m(s_n)\,Y_{\ell'}^{m'}(s_n)\\
[A_{jk}^\varepsilon]_{\ell\ell'}^{mm'} &= \qquad\qquad\qquad\quad - \frac{4\pi\ell'}{2\ell'+1}\sum_{n=1}^{N_{\mathrm{grid}}} w_n\,U_j^n\,Y_\ell^m(s_n)\,\big(t_n^{jk}\big)^{-(\ell'+1)}\,Y_{\ell'}^{m'}(s_n^{jk})
\end{aligned}$$

where $\{w_n\}$ are the weights associated to the integration points. Since the derivatives are independent of ε, we drop the ε-dependency for ease of notation.

The case of the diagonal blocks yields

$$[\nabla_i A_{jj}]_{\ell\ell'}^{mm'} = \frac{2\pi}{2\ell'+1}\sum_n w_n\,\nabla_i U_j^n\,Y_\ell^m(s_n)\,Y_{\ell'}^{m'}(s_n)$$

so that it only requires the derivatives of the characteristic function. The function U_j is, in practice, a smoothed version of the (discontinuous!) characteristic function, and is defined as

$$U_j(x_j + r_j y) = \begin{cases} 1 - f_j(y) & f_j(y) \le 1 \\ 0 & \text{otherwise} \end{cases} \quad , \qquad f_j(y) = \sum_{k\in N_j} \chi\left(\frac{|x_j + r_j y - x_k|}{r_k}\right)$$

where y varies on $\mathbb{S}^2$ and χ is a regularized characteristic function of $[0,1]$. We conclude that $\nabla_i U_j$ and, consequently, $\nabla_i A_{jj}$ are *a priori* nonzero only when $i \in N_j$ or $i = j$.

The case of the off-diagonal blocks, i.e., $j \neq k$, is more involved since it includes the gradient of the product of three functions, namely

$$[\nabla_i A_{jk}]_{\ell\ell'}^{mm'} = -\frac{4\pi\ell'}{2\ell'+1}\sum_n w_n\,Y_\ell^m(s_n)\,\nabla_i\Big[U_j^n\,\big(t_n^{jk}\big)^{-(\ell'+1)}\,Y_{\ell'}^{m'}(s_n^{jk})\Big] \tag{15}$$

However, since t_n^{jk} and s_n^{jk} depend only upon x_j and x_k, if we assume $i \neq j$ and $i \neq k$, we obtain

$$[\nabla_i A_{jk}]_{\ell\ell'}^{mm'} = -\frac{4\pi\ell'}{2\ell'+1}\sum_n w_n\,Y_\ell^m(s_n)\,\nabla U_j^n\,\big(t_n^{jk}\big)^{-(\ell'+1)}\,Y_{\ell'}^{m'}(s_n^{jk}) \tag{16}$$

Thus, since U_j depends only upon x_i such that $i \in N_j$, we conclude that $\nabla_i A_{jk}$ vanishes whenever $i \neq j$ and $i \neq k$ and $i \notin N_j$. In order to discuss the opposite case, i.e., $i = j$ or $i = k$ or $i \in N_j$, notice that the events $(i = j)$ and $(i = k)$ are mutually exclusive, as are $(i = j)$ and $(i \in N_j)$. We obtain the three subcases $i = j$, and $i = k$, and $i \in N_j$, $i \neq k$, which we address individually.

Standard differentiation implies that

$$\nabla_i \Big[U_j^n \left(t_n^{jk}\right)^{-(\ell'+1)} Y_{\ell'}^{m'}(s_n^{jk}) \Big] = \nabla_i U_j^n \left(t_n^{jk}\right)^{-(\ell'+1)} Y_{\ell'}^{m'}(s_n^{jk}) - \\ + U_j^n \,(\ell'+1) \big(t_n^{jk}\big)^{-(\ell'+2)} \nabla_i t_n^{jk}\, Y_{\ell'}^{m'}(s_n^{jk}) + U_j^n \left(t_n^{jk}\right)^{-(\ell'+1)} \left(D_i\, s_n^{ji}\right)^T \nabla_i Y_{\ell'}^{m'}(s_n^{jk}) \quad (17)$$

where D_i emphasizes that the gradient of the vector quantity s_j^{jk} is indeed its Jacobian matrix and where the extra subscripts refer to the variables with respect to which differentiation is taken. We proceed to evaluate $\nabla_i t_n^{jk}$ and $D_i\, s_n^{jk}$. When $i = j$, differentiation implies

$$\nabla_j t_n^{jk} = \frac{s_n^{jk}}{r_k} \qquad , \qquad D_j\, s_n^{jk} = \frac{I - s_n^{jk} \otimes s_n^{jk}}{|x_j + r_j s_n - x_k|^3}$$

where I is the identity matrix and $\otimes$ indicates the outer product. We remark that the Jacobian matrix $D_j\, s_n^{jk}$ is symmetric, so that the transpose in (17) is redundant. Due to the particular relation between x_j and x_k, we obtain $\nabla_j\, t_n^{jk} = -\nabla_k\, t_n^{jk}$ and $D_j\, s_n^{jk} = -D_k\, s_n^{jk}$. We can therefore analogously derive the case $i = k$ and those relationships imply

$$\nabla_j \Big[U_j^n \left(t_n^{jk}\right)^{-(\ell'+1)} Y_{\ell'}^{m'}(s_n^{jk}) \Big] + \nabla_k \Big[U_j^n \left(t_n^{jk}\right)^{-(\ell'+1)} Y_{\ell'}^{m'}(s_n^{jk}) \Big] = \\ \Big[\nabla_j\, U_j^n + \nabla_k\, U_j^n \Big] \left(t_n^{jk}\right)^{-(\ell'+1)} Y_{\ell'}^{m'}(s_n^{jk})$$

which provide a convenient way of evaluating $[\nabla_k\, A_{jk}]_{\ell\ell'}^{mm'}$ from $[\nabla_j\, A_{jk}]_{\ell\ell'}^{mm'}$. In fact, we obtain the quasi-skew-symmetric relation

$$[\nabla_j\, A_{jk}]_{\ell\ell'}^{mm'} + [\nabla_k\, A_{jk}]_{\ell\ell'}^{mm'} = -\frac{4\pi\ell'}{2\ell'+1} \sum_n w_n\, Y_\ell^m(s_n) \Big[\nabla_j\, U_j^n + \nabla_k\, U_j^n \Big] \left(t_n^{jk}\right)^{-(\ell'+1)} Y_{\ell'}^{m'}(s_n^{jk})$$

for $\nabla_i A_{jk}$. Finally, the case $i \in N_j$, $i \neq k$ reduces to (16).

IV. NUMERICAL EXPERIMENTS

A. Convergence tests

We first verify the implementation of the computation of the forces. Let us denote by $\mathcal{F}_{i,\alpha}$ the α-component of the force $\mathcal{F}_i$ for $\alpha = 1, 2, 3$. Let e_α be the canonical unit vectors of $\mathbb{R}^3$. Then, for any atomic position x_i we consider a sequence $\delta_1, \delta_2, \dots$ and consider the approximate force obtained by finite difference

$$\mathcal{F}_{i,\alpha} \approx \mathcal{F}_{i,\alpha}(\delta_n) = \frac{E_s(x_1, \dots, x_i + \delta_n e_\alpha, \dots, x_M) - E_s(x_1, \dots, x_i, \dots, x_M)}{\delta_n},$$

where we have made explicit the dependency of the solvation energy on the nuclear positions.

In table **??**, we illustrate the RMS of the approximate forces with $\delta_n = x^{-n}$ for caffeine.

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B. Timings

Timings for different molecular structures depending on the number of atoms (i.e. alanine chains, hemoglobin, etc).

V. CONCLUSIONS

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Appendix A: ddPCM discretization

The derivation ddPCM discrete operator A^ε_{jk} rests upon the fact that the spherical harmonics Y^m_ℓ are eigenfunctions of the double layer operator on $\mathbb{S}$, i.e., $\mathcal{D}\, Y^m_\ell = -2\pi/(2\ell + 1)\, Y^m_\ell$, along with the following jump relation for the double layer potential

$$\lim_{\delta \to +0} \big(\tilde{\mathcal{D}}\, Y^m_\ell\big)(y \pm \delta\nu) = \pm 2\pi\, Y^m_\ell(y) + (\mathcal{D}\, Y^m_\ell)(y) \tag{A1}$$

where ν denotes the outward normal at $y \in \mathbb{S}$. We shall employ the invariance by translation and scaling $(\mathcal{D}_j\, \Phi_{\varepsilon,j})(s) = (\mathcal{D}\, \hat{\Phi}_{\varepsilon,j})(y)$, where $y = (s - x_j)/r_j$ and $\hat{\Phi}_{\varepsilon,j}$ is defined on $\mathbb{S}$ through the push-forward-like transformation $\hat{\Phi}_{\varepsilon,j}(y) = \Phi_{\varepsilon,j}(s)$. We begin by discussing the diagonal term $2\pi f_\varepsilon\, \Phi_{\varepsilon,j} - U_j\, \mathcal{D}_j\, \Phi_{\varepsilon,j}$ of (8) where, for brevity, we set $f_\varepsilon = (\varepsilon + 1)/(\varepsilon - 1)$. As customary, in order to obtain a numerical discretization, we multiply by a test function φ and integrate over Γ_j. The change of variable $y = (s - x_j)/r_j$, yields an integral over $\mathbb{S}$ which involves the hatted quantities, namely

$$\int_{\Gamma_j} \left(2\pi f_\varepsilon \, \Phi_{\varepsilon,j} - U_j \, \mathcal{D}_j \, \Phi_{\varepsilon,j}\right) \varphi = 2\pi \, f_\varepsilon \, r_j^2 \int_{\mathbb{S}} \hat{\Phi}_{\varepsilon,j} \, \hat{\varphi} - r_j^2 \int_{\mathbb{S}} \hat{U}_j \, \mathcal{D} \, \hat{\Phi}_{\varepsilon,j} \, \hat{\varphi}$$

We proceed to expand $\hat{\Phi}_{\varepsilon,j}$ as a series of spherical harmonics with coefficients $-[G_j]_{\ell'}^{m'}$, and select as a test function $\hat{\varphi}$ the rescaled spherical harmonic $r_j^{-2} \, Y_\ell^m$. The orthogonality of the spherical harmonics, together with the fact that they are eigenfunctions of the double layer potential, yield

$$\int_{\Gamma_j} \left(2\pi f_\varepsilon \, \Phi_{\varepsilon,j} - U_j \, \mathcal{D}_j \, \Phi_{\varepsilon,j}\right) \varphi =$$

$$= -2\pi \, f_\varepsilon \sum_{\ell',m'} [G_j]_{\ell'}^{m'} \, \delta_{\ell\ell'} \delta_{mm'} - \sum_{\ell',m'} [G_j]_{\ell'}^{m'} \, \frac{2\pi}{2\ell'+1} \int_{\mathbb{S}} \hat{U}_j \, Y_{\ell'}^{m'} \, Y_\ell^m$$

The last step to obtain the diagonal block A_{jj}^ε is to approximate the integral through a suitable quadrature formula with weights $\{w_n\}$ and nodes $\{s_n\}$. Once the numerical quadrature is carried out and the spherical harmonics expansion is truncated, we derive the final expression

$$[A_{jj}^\varepsilon]_{\ell\ell'}^{mm'} = 2\pi \, \frac{\varepsilon+1}{\varepsilon-1} \, \delta_{\ell\ell'} \delta_{mm'} + \frac{2\pi}{2\ell'+1} \sum_{n=1}^{N_{\text{grid}}} w_n \, \hat{U}_j(s_n) \, Y_{\ell'}^{m'}(s_n) \, Y_\ell^m(s_n) \tag{A2}$$

The computation of the off-diagonal term $-U_j \, \tilde{\mathcal{D}}_k \, \Phi_{\varepsilon,k}$ employs again the fact that the double layer operator is invariant under translation and scaling, i.e. $(\tilde{\mathcal{D}}_k \, \Phi_{\varepsilon,k})(x) = (\tilde{\mathcal{D}} \, \hat{\Phi}_{\varepsilon,k})(u)$ where $x \in \mathbb{R}^3 \setminus \overline{\Omega}_k$ and $u = (x - x_k)/r_k$. In particular, when $x \in \Gamma_j$, i.e., $x = s = x_j + r_j y$ for some $y \in \mathbb{S}$, then $u = u(y) = (x_j + r_j y - x_k)/r_k$. As the quantity $U_j \, \tilde{\mathcal{D}}_k \, \Phi_{\varepsilon,k}$ in indeed well-defined on the whole Γ_j, we can proceed as before and obtain

$$\int_{\Gamma_j} U_j(s) \, (\tilde{\mathcal{D}}_k \, \Phi_{\varepsilon,k})(s) \, \varphi(s) \, ds = \int_{\mathbb{S}^2} \hat{U}_j(y) \, (\tilde{\mathcal{D}} \, \hat{\Phi}_{\varepsilon,k})(u(y)) \, Y_\ell^m(y) \, dy =$$

$$= -\sum_{\ell',m'} [G_k]_{\ell'}^{m'} \int_{\mathbb{S}^2} \hat{U}_j(y) \, (\tilde{\mathcal{D}} \, Y_{\ell'}^{m'})(u(y)) \, Y_\ell^m(y) \, dy$$

where $-[G_k]_{\ell'}^{m'}$ are the coefficients of the expansion of $\hat{\Phi}_{\varepsilon,k}$ as a series of spherical harmonics. The function $\tilde{\mathcal{D}} \, Y_{\ell'}^{m'}$ is harmonic on $\mathbb{R}^3 \setminus \overline{B(0,1)}$, so that is has to coincide with the unique harmonic extension of its boundary value. The jump relation (A1), along with the eigenfunction property, provide the boundary value

$$\lim_{\delta \to +0} \left(\tilde{\mathcal{D}} \, Y_{\ell'}^{m'}\right)(y + \delta\nu) = 2\pi \, Y_{\ell'}^{m'}(y) + \left(\mathcal{D} \, Y_{\ell'}^{m'}\right)(y) = \frac{4\pi\ell'}{2\ell +' 1} \, Y_{\ell'}^{m'}(y)$$

and, by elementary notions on harmonic functions, we conclude

$$(\tilde{\mathcal{D}}\, Y_{\ell'}^{m'})(u) = \frac{4\pi\ell'}{2\ell'+1}\,\frac{1}{|u|^{\ell'+1}}\, Y_{\ell'}^{m'}(u/|u|)$$

After truncation the series expansion and performing numerical integration we obtain the final result

$$[A_{jk}]_{\ell\ell'}^{mm'} = -\frac{4\pi\ell'}{2\ell'+1}\sum_{n=1}^{N_{\mathrm{grid}}} w_n\,\hat{U}_j(s_n)\,\frac{1}{|u(s_n)|^{\ell'+1}}\, Y_{\ell'}^{m'}\left(\frac{u(s_n)}{|u(s_n)|}\right)\, Y_\ell^m(s_n) \tag{A3}$$

This concludes the derivation of the ddPCM discretization.

Appendix B: ddCOSMO discretization

Here, just for convenience, we repeat some ddCOSMO equations and derivations. This will not be included in the article.

Definition of operators: Single layer potential:

$$(\tilde{\mathcal{S}}_j\, \sigma^j)(x) = \int_{\Gamma_j} \frac{\sigma^j(s')}{|s'-x|}\, ds' \quad , \quad x \in \Omega_j$$

Single layer operator:

$$(\mathcal{S}_j\, \sigma^j)(s) = \int_{\Gamma_j} \frac{\sigma_j(s')}{|s'-s|}\, ds' \quad , \quad s \in \Gamma_j$$

ddCOSMO-equations: We defined

$$W_j(x) = (\tilde{\mathcal{S}}^j\, \sigma^j)(x) \quad , \quad x \in \Omega_j \qquad ; \qquad W_j(s) = (\mathcal{S}_j\, \sigma^j)(s) \quad , \quad s \in \Gamma_j \tag{B1}$$

and the ddCOSMO-equations become

$$W_j(s) = -U_j(s)\, \Phi_{\varepsilon,j}(s) + \big(1 - U_j(s)\big)\, n_j(s) \sum_{k \in N_j} W_k(s) \qquad s \in \Gamma_j \tag{B2}$$

This is equivalent to

$$(\mathcal{S}_j\, \sigma^j)(s) = -U_j(s)\, \Phi_{\varepsilon,j}(s) + \big(1 - U_j(s)\big)\, n_j(s) \sum_{k \in N_j} (\tilde{\mathcal{S}}_k\, \sigma^k)(s) \qquad s \in \Gamma_j \tag{B3}$$

Mapping on unit sphere: Then, introducing $s = x_j + r_j\hat{s}$ and $s' = x_j + r_j\hat{s}'$, we deduce

$$(\mathcal{S}_j\, \sigma^j)(s) = \int_{\Gamma_j} \frac{\sigma^j(s')}{|s'-s|}\, ds' = \frac{1}{r_j} \int_{\Gamma_j} \frac{\sigma^j(s')}{\left|\frac{s'-x_j}{r_j} - \frac{s-x_j}{r_j}\right|}\, ds' = r_j \int_{\mathbb{S}^2} \frac{\sigma^j\,(x_j + r_j\hat{s}')}{|\hat{s}'-\hat{s}|}\, d\hat{s}',$$

so that

$$(\mathcal{S}_j\, \sigma^j)(x_j + r_j\hat{s}) = r_j(\mathcal{S}_{\mathbb{S}^2}\, \sigma^j(x_j + r_j\cdot))(\hat{s}).$$

In a similar manner, for $x = x_j + r_j\hat{x}$ (and thus $\hat{x} \in B_1(0)$):

$$(\tilde{\mathcal{S}}_j\, \sigma^j)(x) = \int_{\Gamma_j} \frac{\sigma_j(s')}{|s'-x|}\, ds' = r_j \int_{\mathbb{S}^2} \frac{\sigma^j\,(x_j + r_j\hat{s}')}{|\hat{s}'-\hat{x}|}\, d\hat{s}' = r_j(\tilde{\mathcal{S}}\, \sigma^j(x_j + r_j\cdot))(\hat{x}) \quad , \quad x \in \Omega_j.$$

Operators applied to spherical harmonics: We have

$$\left(\mathcal{S}_j\, Y_{\ell,m}\left(\tfrac{\cdot - x_j}{r_j}\right)\right)(s) = r_j(\mathcal{S}_{\mathbb{S}^2}\, Y_{\ell,m})(\hat{s}) = \tfrac{4\pi r_j}{2\ell+1} Y_{\ell,m}\left(\tfrac{s-x_j}{r_j}\right).$$

and

$$\left(\tilde{\mathcal{S}}_j\, Y_{\ell,m}\left(\tfrac{\cdot - x_j}{r_j}\right)\right)(x) = r_j \int_{\mathbb{S}^2} \frac{Y_{\ell,m}}{|\hat{s}' - \hat{x}|}\, d\hat{s}' = \tfrac{4\pi r_j}{2\ell+1}\, |\hat{x}|^\ell\, Y_{\ell,m}\left(\tfrac{\hat{x}}{|\hat{x}|}\right) = \tfrac{4\pi r_j}{2\ell+1}\, \tfrac{|x-x_j|^\ell}{r_j^\ell}\, Y_{\ell,m}\left(\tfrac{x-x_j}{|x-x_j|}\right)$$

Approximation: We now approximate

$$\sigma^j(x_j + r_j\hat{s}) = \frac{1}{r_j}\sum_{\ell,m}[X_j]_\ell^m Y_{\ell,m}(\hat{s}).$$

Observe the scaling by $1/r_j$. That implies that W_j at any point $x \in \overline{\Omega_j}$ is given by

$$W_j(x) = (\tilde{\mathcal{S}}^j\, \sigma^j)(x) = \frac{1}{r_j}\sum_{\ell,m}[X_j]_\ell^m \left(\tilde{\mathcal{S}}_j\, Y_{\ell,m}\left(\tfrac{\cdot - x_j}{r_j}\right)\right)(x) = \sum_{\ell,m}[X_j]_\ell^m\, \tfrac{4\pi}{2\ell+1}\, \tfrac{|x-x_j|^\ell}{r_j^\ell}\, Y_{\ell,m}\left(\tfrac{x-x_j}{|x-x_j|}\right)$$

We will now multiply (B3) by $Y_{\ell',m'}$ and integrate over Γ_j. We start with the left hand side:

$$\begin{aligned}
\int_{\Gamma_j} (\mathcal{S}_j\, \sigma^j)(s)\, Y_{\ell',m'}\left(\tfrac{s-x_j}{r_j}\right)\, ds &= \frac{1}{r_j}\sum_{\ell,m}[X_j]_\ell^m \int_{\Gamma_j} \left(\mathcal{S}_j\, Y_{\ell,m}\left(\tfrac{\cdot - x_j}{r_j}\right)\right)(s)\, Y_{\ell',m'}\left(\tfrac{s-x_j}{r_j}\right)\, ds \\
&= \sum_{\ell,m} \tfrac{4\pi}{2\ell+1}[X_j]_\ell^m \int_{\Gamma_j} Y_{\ell,m}\left(\tfrac{s-x_j}{r_j}\right)\, Y_{\ell',m'}\left(\tfrac{s-x_j}{r_j}\right)\, ds \\
&= \sum_{\ell,m} \tfrac{4\pi r_j^2}{2\ell+1}[X_j]_\ell^m \int_{\mathbb{S}^2} Y_{\ell,m}(\hat{s})\, Y_{\ell',m'}(\hat{s})\, d\hat{s} = \tfrac{4\pi r_j^2}{2\ell'+1}[X_j]_{\ell'}^{m'}
\end{aligned}$$

The first term of the right hand side becomes

$$-\int_{\Gamma_j} U_j(s)\, \Phi_{\varepsilon,j}(s) Y_{\ell',m'}\left(\tfrac{s-x_j}{r_j}\right)\, ds = -r_j^2 \int_{\mathbb{S}^2} U_j(x_j + r_j\hat{s})\, \Phi_{\varepsilon,j}(x_j + r_j\hat{s})\, Y_{\ell',m'}(\hat{s})\, d\hat{s}$$

The second term on the right hand side can be developed as follows

$$\begin{aligned}
&\int_{\Gamma_j} \big(1 - U_j(s)\big)\, n_j(s) \sum_{k\in N_j} (\tilde{\mathcal{S}}_k\, \sigma^k)(s)\, Y_{\ell',m'}\left(\tfrac{s-x_j}{r_j}\right)\, ds \\
&= \sum_{k\in N_j} \frac{1}{r_k} \sum_{\ell,m}[X_k]_\ell^m \int_{\Gamma_j} \big(1 - U_j(s)\big)\, n_j(s)\, \left(\tilde{\mathcal{S}}_k\, Y_{\ell,m}\left(\tfrac{\cdot - x_k}{r_k}\right)\right)(s)\, Y_{\ell',m'}\left(\tfrac{s-x_j}{r_j}\right)\, ds \\
&= \sum_{k\in N_j}\sum_{\ell,m} \tfrac{4\pi}{2\ell+1}[X_k]_\ell^m \int_{\Gamma_j} \big(1 - U_j(s)\big)\, n_j(s)\, \tfrac{|s-x_k|^\ell}{r_k^\ell}\, Y_{\ell,m}\left(\tfrac{s-x_k}{|s-x_k|}\right)\, Y_{\ell',m'}\left(\tfrac{s-x_j}{r_j}\right)\, ds \\
&= r_j^2 \sum_{k\in N_j}\sum_{\ell,m} \tfrac{4\pi}{2\ell+1}[X_k]_\ell^m \int_{\mathbb{S}^2} \big(1 - U_j(x_j + r_j\hat{s})\big)\, n_j(x_j + r_j\hat{s})\, \tfrac{|x_j + r_j\hat{s} - x_k|^\ell}{r_k^\ell}\, Y_{\ell,m}\left(\tfrac{x_j + r_j\hat{s} - x_j k}{|x_j + r_j\hat{s} - x_k|}\right)\, Y_{\ell',m'}(\hat{s})\, d\hat{s}
\end{aligned}$$

Combining all three results yields then the discrete ddCOSMO-equations.

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