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General formulation of polarizable embedding models and of their coupling

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ABSTRACT

We propose a general formalism for polarizable embedding models that can be applied to either continuum or atomistic polarizable models. After deriving such a formalism for both variational and non-variational models, we address the problem of coupling two polarizable models among themselves and to a quantum mechanical (QM) description in the spirit of multiscale quantum chemistry. We discuss general model independent coupling hypotheses and derive coupled polarization equations for all combinations of variational and non-variational models and discuss the embedding contributions to the analytical derivatives of the energy, with a particular focus on the elements of the Fock or Kohn–Sham matrix. We apply the general formalism to the derivation of the working equations for a three-layered fully polarizable QM/MM/continuum strategy using the non-variational atomic multipole optimized energetics for biomolecular application polarizable force field and main-decomposition conductor-like screening model.

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I. INTRODUCTION

Polarizable embedding models^{1–19} (PEMs) are a powerful tool in the arsenal of a computational quantum chemist. Continuum solvation models^{6,13} have been part of the standard quantum chemistry toolbox for more than 20 years and are widely available in the majority of the quantum chemistry software packages. Polarizable molecular mechanics (PMM) based embedding schemes^{14–21} are also rapidly gaining in popularity and are widely employed in the modeling, prediction, and rationalization of spectroscopies, photo-physical and photochemical processes, and reactivity. From a merely formal point of view, atomistic and polarizable embedding models present very strong analogies. Both families of models introduce mutual polarization between the quantum mechanical (QM) density and a polarization density of charge that, in turn, introduces a non-linear term into the QM Hamiltonian.²² The polarization density is obtained by solving a set of polarization equations where the right-hand side is some electrostatic property, which is linear in the QM density. In the vast majority of cases, the polarization equations are also linear. While non-linear models exist, for instance, continuum models based on the Poisson–Boltzmann equation,²³ their application in quantum chemistry is not as widespread as that of their

linear counterparts. We, therefore, focus this contribution on linear models.

In the last decade, various implementations that couple a polarizable continuum model to an atomistic, polarizable embedding strategy have been presented.^{24–32} Coupled multiscale models are attractive as they combine the strengths of both approaches, for instance, by being able at the same time to describe specific, local interactions and take care of long-range electrostatic effects. The formulation and implementation of a polarizable multiscale model comes with some formal difficulties. Deriving the coupled equations requires one to be particularly careful of the way the coupling is treated so that double-counting is avoided and, from a thermodynamical point of view, the total energy of the system takes into account the work required to polarize the environment. Such difficulties are exacerbated when two polarizable schemes are coupled together as the number of mutual polarization interactions to be taken into account increases.

A powerful and general strategy to treat polarizable models relies on a variational formulation,^{22,33} where the polarization energy is expressed as a variational functional of the polarization degrees of freedom. Polarization equations can then be easily derived by imposing that such an energy functional

is stationary with respect to the polarization degrees of freedom.³⁴ This, in turn, makes the derivation of analytical derivatives straightforward.

However, not all polarizable embedding models are based on a variational energy definition.^{35–37} A polarizable model can be non-variational if the interaction energy is defined in terms of an electrostatic property that is different from the one that induces the polarization or if the polarization equations are defined in terms of a non-symmetric matrix or operator. Furthermore, continuum models can be variational in their exact, continuous formulation but lose this property when discretized, as the commutation properties of the integral operators that define the polarization equations are not retained after discretization.^{38–40} For non-variational models, the machinery described in the last paragraph cannot be employed, and the derivation of coupled QM/PEM equations or QM/PEM analytical derivatives can become cumbersome or require *ad hoc* reasoning and complex physical arguments. The situation becomes even more complex when two polarizable models are used in the embedding scheme at the same time. Despite these complications, QM/PEM schemes based on non-variational models are available,^{41,42} sometimes including analytical gradients or higher order derivatives.^{39,43–46} To the best of our knowledge, only one attempt has been done at coupling two non-variational polarizable models, namely, the Atomic Multipole Optimized Energetics for Biomolecular Applications (AMOEBA) force field and the domain-composition formulation of COSMO (ddCOSMO), albeit in a purely classical framework.³⁰ In such an example, the coupling has been achieved using a valid but heuristic argument, where only the AMOEBA polarization was treated as an independent degree of freedom, while the ddCOSMO polarization was introduced always as the formal solution of the ddCOSMO equation. As a consequence, the derivation of analytical derivatives was very cumbersome and needed to be verified numerically in order to validate the heuristic coupling arguments.

In this contribution, we define rigorously the characteristic of a polarizable model that makes it variational, and we discuss a general Lagrangian strategy to deal with non-variational cases. We then deal with the problem of coupling two polarizable models in general terms, including when two non-variational models are involved. In order to do this, we first discuss how to describe the interaction between polarization degrees of freedom in a general way and give a precise definition of the coupling hypotheses. We finally propose a general Lagrangian that can be used to obtain the coupled equations and the analytical derivatives of the energy. Finally, to show the potentialities of such a general strategy, we derive the coupled QM/classical equations for a QM/AMOEBA/ddCOSMO multiscale model and compare our results to the one already obtained by us. Thanks to the generality of the formalism developed in this contribution, even the coupling of the two aforementioned models can be achieved in a simple, straightforward way.

II. GENERAL THEORY OF POLARIZABLE EMBEDDING MODELS

In this section, we derive a general formalism for a PEM coupled to a quantum mechanical level of theory based on the

self-consistent field (SCF) algorithm, such as Hartree–Fock (HF) or Kohn–Sham (KS) density functional theory (DFT). First, we consider a PEM based on a variational energy functional, and then we detail the case of non-variational models, with particular attention to the connection between the two and the hypotheses that a model needs to satisfy to be variational.

In general, a PEM presents two densities of charge, a fixed one M , for instance, a collection of point charges or higher order multipoles, and a polarization one X . Assuming that the PEM is linear, the polarization density X is determined by solving a linear equation

$$AX = -\Theta^{\text{MM}}(M) - \Theta^{\text{QM}}(\rho), \quad (1)$$

where A is a model-dependent polarization matrix and Θ is a linear function of either the classical density M or the QM one ρ . Note that the QM density ρ is the sum of a nuclear and an electronic part. For the sake of simplicity, we assume here that we are working with the discretized version of PEMs that are formulated in terms of a continuous polarization density, i.e., the polarization degrees of freedom X are always a finite collection of values or, in other words, the vector space where we are working is \mathbb{R}^n for some finite $n \in \mathbb{N}$, which, endowed with the canonical scalar product $\langle \cdot, \cdot \rangle$, is a Hilbert space. Finally, we also assume that all the densities interact in a pairwise, classical fashion, i.e., the interactions between the various densities can be written as bilinear forms

$$\begin{aligned} E(\rho, M) &= \langle \Phi(\rho), M \rangle, \\ E(\rho, X) &= \langle \Psi^{\text{QM}}(\rho), X \rangle, \\ E(M, X) &= \langle \Psi^{\text{MM}}(M), X \rangle. \end{aligned} \quad (2)$$

In Eq. (2), the linear function $\Phi(\rho)$ is the appropriate electrostatic property that describes the interaction of the QM density ρ with the fixed classical one M (e.g., if M is a distribution of charges, Φ is the electrostatic potential produced by the QM density at the aforementioned charges). Analogously, Ψ is the linear function of either the QM density ρ or the fixed, classical one M that describes the interaction of such density with the induced polarization density X . Applying the functions Θ , Ψ , and Φ to the QM density ρ results in two contributions, one from the nuclei and one from the electronic density. As an example, we consider the function

$$\Theta(\rho) = \Theta^{\text{nuc}}(Z) + \sum_{\mu\nu} P_{\mu\nu} \Theta_{\mu\nu}, \quad (3)$$

where Z is the collection of nuclei, $P_{\mu\nu}$ is the $\mu\nu$ element of the electronic density, and $\Theta_{\mu\nu}$ is a one-electron integral. Analogous expressions can be written for Ψ and Φ . However, in the following, we put $\Theta = \Theta^{\text{QM}} + \Theta^{\text{MM}}$ and $\Psi = \Psi^{\text{QM}} + \Psi^{\text{MM}}$ to keep the notation simple. For the sake of generality, we note here that some polarizable models impose additional constraints on the polarization degrees of freedom—for instance, in fluctuating charge models, a total charge constraint has to be explicitly considered. From a practical point of view, assuming that the constraints are linear, this has little effect on the theory, as the constraints are easily handled by using a set of Lagrange multipliers. In order to keep the notation as simple as possible, we will ignore this possibility, which can be easily introduced without altering the overall formalism.

In Table I, we provide a few model-specific definitions of all the aforementioned quantities. More detailed expressions can be found in the relevant literature.

A. Variational embedding models

A polarizable model is variational if the following two properties hold:

1. The linear functions Θ and Ψ coincide, i.e., $\Theta^{\text{MM}}(M) = \Psi^{\text{MM}}(M)$ and $\Theta^{\text{QM}}(\rho) = \Psi^{\text{QM}}(\rho)$.
2. The matrix A is symmetric and positive definite.

If these two hypotheses are satisfied, then the unique solution to the polarization equation (1) is also the unique minimizer of the following energy functional:

$$\mathcal{E}^{\text{pol}}(X) = \frac{1}{2} \langle X, AX \rangle + \langle X, \Psi \rangle. \quad (4)$$

The main advantage of having a variational formulation is that analytical derivatives of the polarization energy can be obtained trivially. In fact, as the functional in Eq. (4) is stationary with respect to X , one simply gets, differentiating with respect to an arbitrary parameter ξ ,

$$\frac{d\mathcal{E}^{\text{pol}}(X)}{d\xi} = \frac{\partial\mathcal{E}^{\text{pol}}(X)}{\partial\xi} = \frac{1}{2} \left\langle X, \frac{\partial A}{\partial\xi} X \right\rangle + \left\langle X, \frac{\partial\Psi}{\partial\xi} \right\rangle. \quad (5)$$

Let us now consider the coupled QM/PEM equations, where the QM subsystem is described at the SCF level of theory. The total, multi-scale energy is the sum of the QM energy of the isolated QM subsystem, the self-interaction energy of the classical charge distribution M , the interaction energy of M and ρ , and the energy functional in Eq. (4), i.e.,

$$\mathcal{E}(\rho, X) = \text{tr } hP + \frac{1}{2} \text{tr } PG(P) + E^{\text{nuc}} + E^{\text{self}}(M) + \langle \Phi(\rho), M \rangle + \frac{1}{2} \langle X, AX \rangle + \langle X, \Psi \rangle. \quad (6)$$

TABLE I. Expressions for the functions Θ and Ψ , for the matrix A , and for the energy in the case of various PEMs using the notation that appears in the literature. The non-variational models are marked with a †. FQ: fluctuating charges and IPD: induced point dipoles. V and E are, respectively, the electric potential and field, Φ and Ψ are the ddCOSMO functions (see Ref. 41 for the detailed expressions), and $\tilde{\Psi}$ is defined as Ψ , but it is not scaled by the COSMO factor. χ is the collection of atomic electronegativities.¹⁴ S and D are the discretized single and double layer operators of pulsed-code modulation (PCM) theory,^{39,40} note that D is discretized differently in the case of ddPCM.⁴⁹ L is the ddCOSMO matrix.⁴⁴ J and T are, respectively, the interaction matrices between fluctuating charges²⁹ and induced dipoles.⁵² σ is the discretized surface charge of PCM, that is, the collection of the PCM charges,^{38–40} and X is the representation of the reaction potential in the case of ddCOSMO.⁴⁴ q collects the fluctuating charges.²⁹ μ and μ_d are induced dipole collections.^{51,53}

Model	Θ	Ψ	A	Energy
COSMO ⁴⁷	V	V	S	$1/2 \langle \sigma, V \rangle$
IEFPCM ^{†48}	V	V	$(2\pi - D)^{-1} \left(2\pi \frac{\epsilon + 1}{\epsilon - 1} - D \right) S$	$1/2 \langle \sigma, V \rangle$
ddCOSMO ^{†36,41}	Φ	Ψ	L	$1/2 \langle \Psi, X \rangle$
ddPCM ^{†46,49}	Φ	$\tilde{\Psi}$	$(2\pi - D)^{-1} \left(2\pi \frac{\epsilon + 1}{\epsilon - 1} - D \right) L$	$1/2 \langle \tilde{\Psi}, X \rangle$
FQ ^{12,50}	$V + \chi$	$V + \chi$	J	$1/2 \langle q, V + \chi \rangle$
IPD ⁵¹	$-E(\rho) - E(q)$	$-E(\rho) - E(q)$	T	$-1/2 \langle \mu, E(\rho) + E(q) \rangle$
AMOEBa ^{35,42}	$-E(\rho) - E_p(M)$	$-E(\rho) - E_d(M)$	T	$-1/2 \langle \mu_d, E(\rho) + E_p(M) \rangle$

In order to derive the coupled QM/PEM equations, we just differentiate Eq. (6) with respect to a density matrix element $P_{\mu\nu}$ to obtain the QM/PEM Fock (KS) matrix \tilde{F} , which defines the Roothaan equations, and with respect to the polarization degrees of freedom in order to obtain the polarization equations,

$$\begin{aligned} \tilde{F}(P, X) &= \frac{\partial\mathcal{E}(\rho, X)}{\partial P_{\mu\nu}} = h_{\mu\nu} + G_{\mu\nu}(P) + \langle \Phi_{\mu\nu}, M \rangle + \langle \Psi_{\mu\nu}, X \rangle, \\ \tilde{F}(P, X)C &= \text{SCE}, \\ \frac{\partial\mathcal{E}(\rho, X)}{\partial X} &= AX + \Psi = 0. \end{aligned} \quad (7)$$

The total energy can then be computed using Eq. (6), where we substitute the solution to the coupled equations (7). It is worth here to note that the polarization energy functional (4), computed in its minimum, i.e., for X satisfying the polarization equations, simplifies into the following expression for the polarization energy:

$$E^{\text{pol}} = \frac{1}{2} \langle X, \Psi \rangle. \quad (8)$$

B. Non-variational embedding models

In Sec. II A, we stated the conditions under which a PEM is variational, which are not always satisfied. The main issue with non-variational models is the computation of analytical derivatives of the energy, including contributions to the Fock (KS) matrix. If the energy is not variational in the polarization density, computing the analytical derivatives requires the computation of additional terms coming from the chain rule. Fortunately, as shown by Poier *et al.* in Ref. 37, it is always possible to introduce a Lagrangian for these models, which is stationary when the polarization equations are solved. The price to pay is that one needs to introduce an auxiliary polarization degree of freedom, which, in practice, means that, in order to compute an analytical derivative, two independent sets of equations need to be solved. Let us detail this case.

Let us assume that the polarization equations are defined in terms of a non-symmetric matrix (operator) A , according to Eq. (1), and Θ is different from Ψ . In this case, the variational Lagrangian is as follows:

$$\mathcal{L}^{\text{pol}}(X, S) = \frac{1}{2} \langle X, \Psi \rangle + \frac{1}{2} \langle S, AX + \Theta \rangle, \quad (9)$$

where S are Lagrange multipliers. The corresponding Euler-Lagrange equations are

$$\frac{\partial \mathcal{L}^{\text{pol}}}{\partial S} = AX + \Theta = 0, \quad \frac{\partial \mathcal{L}^{\text{pol}}}{\partial X} = A^\dagger S + \Psi = 0. \quad (10)$$

When computed in its stationary point, the Lagrangian value that corresponds to the polarization energy. We note that the Euler-Lagrange equation obtained by differentiating the Lagrangian with respect to the Lagrange multipliers S enforces the polarization equations. Differentiating with respect to X gives rise to a set of adjoint equations that need to be solved in order to compute the derivatives of the energy in an efficient way. Once these have been solved, the energy derivatives with respect to a generic parameter ξ are assembled as

$$\frac{d\mathcal{L}^{\text{pol}}}{d\xi} = \frac{1}{2} \left\langle X, \frac{\partial \Psi}{\partial \xi} \right\rangle + \frac{1}{2} \left\langle S, \frac{\partial A}{\partial \xi} X + \frac{\partial \Theta}{\partial \xi} \right\rangle, \quad (11)$$

which does not involve derivatives of either the polarization degrees of freedom or the Lagrange multipliers. We note here that there is an evident analogy with the so-called “Z-vector” method⁵⁴ in quantum chemistry.

Equation (11) is the key to solve the problem of coupling a non-variational polarizable embedding model to the HF (DFT) method. In fact, the total Fock (KS) matrix can always be written as the derivative of the total energy Lagrangian [i.e., the polarization Lagrangian plus the HF (DFT) energy plus the interaction energy between the static distribution M and the QM density] with respect to density, which can be computed by introducing the Lagrangian in Eq. (9), i.e.,

$$\tilde{F}_{\mu\nu} = \frac{\partial \mathcal{L}(P, X, S)}{\partial P_{\mu\nu}} = h_{\mu\nu} + G_{\mu\nu}(P) + \langle M, \Phi_{\mu\nu} \rangle + \frac{1}{2} \langle X, \Psi_{\mu\nu} \rangle + \frac{1}{2} \langle S, \Theta_{\mu\nu} \rangle, \quad (12)$$

where we have used the same notation as in Eq. (3) for the one-electron integrals. From a practical point of view, Eq. (12) implies that for a non-variational embedding model, at each SCF iteration, one has to solve two linear systems of polarization equations, one for X and one for S , effectively doubling the computational cost associated with embedding. The same procedure applies to the computation of any other analytical energy derivatives included, as detailed in Ref. 37, the computation of the forces.

We conclude this section by considering the connection between the Lagrangian and variational formulations. Starting from the Lagrangian in Eq. (9) and imposing the variational conditions, i.e., $\Theta = \Psi$ and $A^\dagger = A$, we get

$$\mathcal{L}^{\text{pol}}(X, S) = \frac{1}{2} \langle X, \Psi \rangle + \frac{1}{2} \langle S, AX + \Psi \rangle. \quad (13)$$

Let us now consider the associated Euler-Lagrange equations. Looking at the adjoint equation, we get

$$\frac{\partial \mathcal{L}^{\text{pol}}}{\partial S} = AX + \Psi = 0, \quad \frac{\partial \mathcal{L}^{\text{pol}}}{\partial X} = A^\dagger S + \Psi = 0. \quad (14)$$

As $A^\dagger = A$, X and S satisfy the same linear equation and are therefore equal due to the unicity of the solution. By setting $S = X$ in Eq. (13), we recover the variational energy functional in Eq. (4) and, therefore, the two formulations are consistent with each other.

III. COUPLING TWO POLARIZABLE MODELS

Coupling two polarizable models, in particular, an atomistic model with a continuum one, is an attractive task, as it allows one to combine the strengths of an atomistic model, namely, its ability to describe specific interactions and a strongly anisotropic environment, with the ones of a continuum model, i.e., taking care in a very effective way of long-range interactions. In this section, we explore in a general fashion the coupling of variational and non-variational models.

A. Coupling two variational models

Let X and Y be the polarization degrees of freedom of the two models, respectively, and let

$$\begin{aligned} \mathcal{E}_1^{\text{pol}}(X) &= \frac{1}{2} \langle X, AX \rangle + \langle X, \Psi_1 \rangle, \\ \mathcal{E}_2^{\text{pol}}(Y) &= \frac{1}{2} \langle Y, BY \rangle + \langle Y, \Psi_2 \rangle \end{aligned} \quad (15)$$

be the corresponding energy functionals, where, for brevity, we put again $\Psi_1 = \Psi_1^{\text{MM}}(M) + \Psi_1^{\text{QM}}(\rho)$ and $\Psi_2 = \Psi_2^{\text{MM}}(M) + \Psi_2^{\text{QM}}(\rho)$. In order to couple the two models, the only ingredient needed is the interaction energy between the two polarization densities. Note that, for notation simplicity, we do not distinguish the non-polarizable distributions M_1 and M_2 associated with the two models, as the distinction is anyways inessential. We assume that the interaction between X and Y can be expressed as a bilinear form

$$E^{\text{int}}(X, Y) = \langle Y, \Omega X \rangle \quad (16)$$

and that the matrix Ω describes a positive definite interaction. Both assumptions are trivially satisfied if the interaction is the classic Coulombic interaction, which is normally always the case. Under these hypotheses, a global, variational energy functional can be simply obtained as the sum of the QM energy, the two non-interacting energy functionals in Eq. (15), and the interaction energy in Eq. (16),

$$\begin{aligned} \mathcal{E}(\rho, X, Y) &= E^{\text{QM}}(\rho) + E^{\text{self}}(M) + \langle \Phi(\rho), M \rangle + \frac{1}{2} \langle X, AX \rangle \\ &+ \langle X, \Psi_1 \rangle + \frac{1}{2} \langle Y, BY \rangle + \langle Y, \Psi_2 \rangle + \langle Y, \Omega X \rangle. \end{aligned} \quad (17)$$

The coupled polarization equations are easily obtained by imposing the stationarity conditions of the functional in Eq. (17) with respect to both X and Y . Rearranging, the following linear equations are obtained:

$$\begin{pmatrix} A & \Omega^\dagger \\ \Omega & B \end{pmatrix} \begin{pmatrix} X \\ Y \end{pmatrix} = - \begin{pmatrix} \Psi_1 \\ \Psi_2 \end{pmatrix}. \quad (18)$$

Furthermore, the embedded Fock (KS) matrix is

$$\begin{aligned} \tilde{F}(P, X, Y) = \frac{d\mathcal{E}(\rho, X)}{dP_{\mu\nu}} &= h_{\mu\nu} + G_{\mu\nu}(P) + \langle \Phi_{\mu\nu}, M \rangle \\ &+ \langle \Psi_{1,\mu\nu}, X \rangle + \langle \Psi_{2,\mu\nu}, Y \rangle. \end{aligned} \quad (19)$$

The variational formalism makes it straightforward to achieve full mutual polarization between all the involved densities, as well as to derive the working equations. The variational strategy has already been used in the literature to couple two variational PEMS, for instance, the fluctuating charge model (FCM) and C-PCM.²⁹

B. Coupling a variational model to a non-variational one

Let us now assume that the first model is variational, while the second is not, i.e., they are described, respectively, by the energy functional and Lagrangian

$$\begin{aligned} \mathcal{E}_1^{\text{pol}}(X) &= \frac{1}{2} \langle X, AX \rangle + \langle X, \Psi_1 \rangle, \\ \mathcal{L}_2^{\text{pol}}(Y, Z) &= \frac{1}{2} \langle Y, \Psi_2 \rangle + \frac{1}{2} \langle Z, BY + \Theta_2 \rangle. \end{aligned} \quad (20)$$

We introduce the following coupling hypotheses:

- The two polarization densities interact with the same bilinear form used for the variational case, i.e., we add to the total interaction energy a contribution

$$\mathcal{E}^{\text{int}} = \frac{1}{2} \langle Y, \Omega X \rangle,$$

where the 1/2 factor has been introduced for later convenience.

- We enforce mutual polarization by adding an explicit dependence on X to the right-hand side of the equation for Y . This is achieved by replacing Θ_2 with $\Theta_2 + \Xi X$, where Ξ is a matrix, i.e., the dependence on X is linear.

We remark that while the first condition modifies the total energy, the second one modifies the constraint imposed on the non-variational model: this is consistent with the mixed nature of the two models that need to be coupled. In other words, the energy functional for X is modified with a contribution that depends on Y , while the Lagrangian condition for Y is modified with a term that depends linearly on X . The two coupled models are thus described by the following global polarization Lagrangian:

$$\begin{aligned} \mathcal{L}^{\text{pol}}(X, Y, Z) &= \frac{1}{2} \langle X, AX \rangle + \langle X, \Psi_1 \rangle + \frac{1}{2} \langle Y, \Omega X \rangle \\ &+ \frac{1}{2} \langle Y, \Psi_2 \rangle + \frac{1}{2} \langle Z, BY + \Theta_2 + \Xi X \rangle. \end{aligned} \quad (21)$$

By differentiating with respect to X , Y , and Z and by imposing the stationarity conditions, we get the following set of coupled equations:

$$\begin{pmatrix} A & \frac{1}{2}\Omega^\dagger & \frac{1}{2}\Xi^\dagger \\ \Omega & 0 & B^\dagger \\ \Xi & B & 0 \end{pmatrix} \begin{pmatrix} X \\ Y \\ Z \end{pmatrix} = - \begin{pmatrix} \Psi_1 \\ \Psi_2 \\ \Theta_2 \end{pmatrix}. \quad (22)$$

The matrix in Eq. (22) is almost symmetric, where the symmetry is broken by the presence of the 1/2 factors. Such factors are needed in order to maintain a consistent definition of the interaction energy for each model taken independently and cannot be absorbed into other quantities in the Lagrangian without altering the definition of the right-hand sides for the non-variational model. However, a symmetric matrix can be easily obtained by solving for $Y/2$ and $Z/2$,

$$\begin{pmatrix} A & \Omega^\dagger & \Xi^\dagger \\ \Omega & 0 & 2B^\dagger \\ \Xi & 2B & 0 \end{pmatrix} \begin{pmatrix} X \\ \frac{1}{2}Y \\ \frac{1}{2}Z \end{pmatrix} = - \begin{pmatrix} \Psi_1 \\ \Psi_2 \\ \Theta_2 \end{pmatrix}. \quad (23)$$

It is again interesting to check the consistency of the Lagrangian in Eq. (21) with the energy functional in Eq. (17) by imposing the variational conditions to Eq. (21). The condition $\Psi_2 = \Theta_2$ applied to our coupling hypotheses implies that $\Omega = \Xi$, and the symmetry of the B matrix implies that $Y = Z$. Therefore, once again, the two formulations are consistent.

We conclude this section deriving the embedding contribution to the Fock matrix, which is obtained by differentiating the Lagrangian in Eq. (21) with respect to the density matrix. We first note that, thanks to the stationarity conditions imposed, its analytical derivative with respect to an arbitrary parameter ξ is given by

$$\begin{aligned} \frac{d\mathcal{L}^{\text{pol}}}{d\xi} &= \frac{1}{2} \left\langle X, \frac{\partial A}{\partial \xi} X \right\rangle + \left\langle X, \frac{\partial \Psi_1}{\partial \xi} \right\rangle + \frac{1}{2} \left\langle Y, \frac{\partial \Omega}{\partial \xi} X \right\rangle \\ &+ \frac{1}{2} \left\langle Y, \frac{\partial \Psi_2}{\partial \xi} \right\rangle + \frac{1}{2} \left\langle Z, \frac{\partial B}{\partial \xi} Y + \frac{\partial \Theta_2}{\partial \xi} + \frac{\partial \Xi}{\partial \xi} X \right\rangle. \end{aligned} \quad (24)$$

This expression can then be used to derive the Fock matrix, which takes into account also the QM energy and the interaction of the QM density with the fixed distribution M ,

$$\tilde{F} = h_{\mu\nu} + G_{\mu\nu}(P) + \langle \Phi_{\mu\nu}, M \rangle + \langle \Psi_{1,\mu\nu}, X \rangle + \frac{1}{2} \langle \Psi_{2,\mu\nu}, Y \rangle + \frac{1}{2} \langle \Theta_{2,\mu\nu}, Z \rangle. \quad (25)$$

To the best of our knowledge, the use of a mixed Lagrangian/variational strategy as the one presented in this section has not been reported in the literature. Nevertheless, variational and non-variational models have been coupled before, including in a multiscale QM/classical context.^{27,30,55} The strategy introduced here allows one to derive the coupled equations in a black-box and in a rigorous way, easing the way of new developments in this direction. An example, namely, the derivation of the coupled MMPol/ddCOSMO equations, can be found in Sec. IV.

C. Coupling two non-variational models

The most general task, i.e., coupling two non-variational models, requires some general considerations:

- Relaxing the variational hypotheses on the first model doubles the overall number of degrees of freedom; this means that the second model needs to be coupled to both the polarization degrees of freedom X and the corresponding Lagrange multipliers S . This requires four degrees of freedom within the second model, namely, Y^X , Z^X , Y^S , and Z^S .
- The equations for S and for X need to be uncoupled, as those for the couple Y^X and Z^X and those for the couple Y^S and Z^S , as they correspond to a set of polarization equations and a set of Lagrange multipliers equations that are independent due to the linearity of the overall problem. This requires that no term in the Lagrangian can couple Y^X with X or Y^S with S .
- The same linear coupling hypotheses used for the previous cases need to hold, i.e., all couplings are bilinear forms.

The latter condition needs to take into account that there are two polarizations for the second model and that they need to interact with both X and S , which, together with the second consideration, leads to the following expression for the interaction energy:

$$E^{\text{int}} = \frac{1}{4}(\langle Y^S, \Omega X \rangle + \langle Y^X, \Omega S \rangle). \quad (26)$$

Starting from these hypotheses, the following Lagrangian can be written as

$$\begin{aligned} \mathcal{L}^{\text{pol}}(X, S, Y^X, Z^X, Y^S, Z^S) = & \frac{1}{2}\langle X, \Psi_1 \rangle + \frac{1}{4}\langle Y^X + Y^S, \Psi_2 \rangle \\ & + \frac{1}{4}(\langle Y^S, \Omega X \rangle + \langle Y^X, \Omega S \rangle) \\ & + \frac{1}{2}\langle S, AX + \Theta_1 \rangle + \frac{1}{4}\langle Z^S, BY^X + \Theta_2 + \Xi X \rangle \\ & + \frac{1}{4}\langle Z^X, BY^S + \Theta_2 + \Xi S \rangle. \end{aligned} \quad (27)$$

The first two terms in the Lagrangian represent the interaction energy of the two PEMs with the sources, the third term is the interaction energy between the polarizations, and all the latter terms enforce the constraints on the polarizations. The first set of coupled Euler–Lagrange equations is obtained by differentiation with respect to S , Y^S , and Z^S ,

$$\begin{pmatrix} A & \Omega^\dagger & \Xi^\dagger \\ \Omega & 0 & 2B^\dagger \\ \Xi & 2B & 0 \end{pmatrix} \begin{pmatrix} X \\ \frac{1}{2}Y^X \\ \frac{1}{2}Z^X \end{pmatrix} = - \begin{pmatrix} \Theta_1 \\ \Psi_2 \\ \Theta_2 \end{pmatrix}, \quad (28)$$

where we use the symmetrized form of the equations as in Eq. (23). By differentiating with respect to X , Y^X , and Z^X , we get the second set of coupled Euler–Lagrange equations,

$$\begin{pmatrix} A^\dagger & \Omega^\dagger & \Xi^\dagger \\ \Omega & 0 & 2B^\dagger \\ \Xi & 2B & 0 \end{pmatrix} \begin{pmatrix} S \\ \frac{1}{2}Y^S \\ \frac{1}{2}Z^S \end{pmatrix} = - \begin{pmatrix} \Psi_1 \\ \Psi_2 \\ \Theta_2 \end{pmatrix}. \quad (29)$$

We note that, consistently with S , Y^S , and Z^S playing the role of Lagrange multipliers, the matrix in Eq. (29) is the adjoint of the one in Eq. (28). The two linear systems (28) and (29) fully determine the mutually polarized densities of the two models and both need to be solved even to compute the energy, as the latter depends on Y^X and Y^S . The consistency of the general Lagrangian with the variational subcases is easily checked. Let us assume that the variational hypotheses hold for the first model. We see immediately that as $A^\dagger = A$ and $\Psi_1 = \Theta_1$, the two linear systems (28) and (29) become identical, and thus, we get $S = X$, $Y^S = Y^X$, and $Z^S = Z^X$. By inserting this result in Lagrangian (27), we get the Lagrangian in Eq. (21), which we have already shown to be consistent with the fully variational case. Let us derive now the analytical derivatives of the energy with respect to an arbitrary parameter ξ ,

$$\begin{aligned} \frac{d\mathcal{L}}{d\xi} = & \frac{1}{2}\left\langle X, \frac{\partial\Psi_1}{\partial\xi} \right\rangle + \frac{1}{4}\left\langle Y^X + Y^S, \frac{\partial\Psi_2}{\partial\xi} \right\rangle \\ & + \frac{1}{4}\left(\left\langle Y^S, \frac{\partial\Omega}{\partial\xi} X \right\rangle + \left\langle Y^X, \frac{\partial\Omega}{\partial\xi} S \right\rangle\right) \\ & + \frac{1}{2}\left\langle S, \frac{\partial A}{\partial\xi} X + \frac{\partial\Theta_1}{\partial\xi} \right\rangle + \frac{1}{4}\left\langle Z^S, \frac{\partial B}{\partial\xi} Y^X + \frac{\partial\Theta_2}{\partial\xi} + \frac{\partial\Xi}{\partial\xi} X \right\rangle \\ & + \frac{1}{4}\left\langle Z^X, \frac{\partial B}{\partial\xi} Y^S + \frac{\partial\Theta_2}{\partial\xi} + \frac{\partial\Xi}{\partial\xi} S \right\rangle. \end{aligned} \quad (30)$$

We can once again get the Fock (KS) matrix including the contribution of the polarizable environment as a derivative of Lagrangian (27) with respect to the density matrix after adding the QM energy and the interaction energy between the fixed distribution M and the QM density. We get

$$\begin{aligned} \tilde{F}_{\mu\nu} = & h_{\mu\nu} + G_{\mu\nu}(P) + \langle \Phi_{\mu\nu}, M \rangle + \frac{1}{2}(\langle \Psi_{1,\mu\nu}, X \rangle + \langle \Theta_{1,\mu\nu}, S \rangle) \\ & + \frac{1}{4}(\langle \Psi_{2,\mu\nu}, X^Y + Y^S \rangle + \langle \Theta_{2,\mu\nu}, S^Y + S^Z \rangle). \end{aligned} \quad (31)$$

The general strategy presented in this section is applied in Sec. IV to the derivation of the coupled QM/AMOEBA/ddCOSMO equations.

D. Quasi-variational models

As a note to the whole section, it is interesting to consider the case of a non-variational model in which the matrix A is symmetric. If the non-variational polarization equations are defined in terms of a symmetric matrix, the Lagrangian in Eq. (9) can be rewritten in a form where X and S appear in a symmetric fashion. We call a PEM defined in terms of a symmetric matrix *quasi-variational*. Assuming that $A = A^\dagger$, in fact, the polarization X , its Lagrangian S , and their sum $X + S$ satisfy independently variational conditions, i.e., as noted in Ref. 30, they minimize the following three energy functionals:

$$\mathcal{E}(X) = \frac{1}{2}\langle X, AX \rangle + \langle X, \Theta \rangle, \quad (32)$$

$$\mathcal{E}(S) = \frac{1}{2}\langle S, AS \rangle + \langle S, \Psi \rangle, \quad (33)$$

$$\mathcal{E}(X + S) = \frac{1}{2}\langle X + S, A(X + S) \rangle + \langle X + S, \Theta + \Psi \rangle. \quad (34)$$

We can therefore combine the three functionals into the following Lagrangian of X and S :

$$2\mathcal{L}(X, S) = \frac{1}{2}\langle X + S, A(X + S) \rangle + \langle X + S, \Psi + \Theta \rangle - \left(\frac{1}{2}\langle X, AX \rangle + \langle \Theta, X \rangle \right) - \left(\frac{1}{2}\langle S, AS \rangle + \langle \Psi, S \rangle \right). \quad (32)$$

As it can easily be verified, imposing the stationarity condition on Eq. (32), one gets Eq. (10), where in the equation for S , there is no adjoint as the matrix is symmetric. Besides the fact that Eq. (32) is manifestly symmetrical, it is written as the difference of three variational energy functionals. This allows one to extend the validity of such a Lagrangian also for values of X and S that do not solve the corresponding equations, which can be used, for instance, to define an extended Lagrangian used to propagate X and S during a molecular dynamics simulation in the spirit of Car–Parrinello MD.^{29,56,57} Therefore, quasi-variational models enjoy some of the properties of variational ones; however, they keep being associated with two sets of polarization degrees of freedom and, therefore, a doubled computational cost with respect to the strictly variational models.

Let us now consider the coupling between a quasi-variational model and a non-variational one, as it is the case for the AMOEBA polarizable force field and the ddCOSMO CSM. The Lagrangian

$$2\mathcal{L}_{qv}^{pol} = \frac{1}{2}\langle X + S, A(X + S) \rangle + \langle X + S, \Theta_1 + \Psi_1 \rangle + \frac{1}{2}\langle Y^X + Y^S, \Omega(X + S) + 2\Psi_2 \rangle + \frac{1}{2}\langle Z^X + Z^S, B(Y^X + Y^S) + 2\Theta_2 + \Xi(X + S) \rangle - \left(\frac{1}{2}\langle X, AX \rangle + \langle X, \Theta_1 \rangle + \frac{1}{2}\langle Y^X, \Omega X + \Psi_2 \rangle + \frac{1}{2}\langle Z^X, BY^X + \Theta_2 + \Xi X \rangle - \left(\frac{1}{2}\langle S, AS \rangle + \langle S, \Psi_1 \rangle + \frac{1}{2}\langle Y^S, \Omega S + \Psi_2 \rangle + \frac{1}{2}\langle Z^S, BY^S + \Theta_2 + \Xi S \rangle \right) \right) \quad (33)$$

gives the same Euler–Lagrange equations (28) and (29) with the only difference that, in Eq. (29), the A matrix does not need the adjoint sign, as it is symmetric. In other words, the matrix defining both sets of equations is the same. The Lagrangian in Eq. (33) is symmetric in X and S , and in a way, they are coupled to the second model. Furthermore, it can also be viewed as the combination of three quasi-variational Lagrangians for the sum of X and S , X and S , respectively, each one coupled accordingly with the second model. In other words, some of the same conclusions hold than for an uncoupled quasi-variational model; it is, in principle, possible to propagate the degrees of freedom X and S during a MD simulation in a Car–Parrinello fashion. However, at each step, the equations for the second model have to be solved exactly.

The quasi-variational Lagrangian in Eq. (33) is the result that most closely resembles in spirit the energy functional proposed by one of us and co-workers in Ref. 30, where the degrees of freedom of the second model were not considered explicitly but rather inserted in an energy expression under the condition that the corresponding polarization and adjoint equations had been solved. As

the Euler–Lagrange obtained here, as well as the analytical derivatives that can be easily derived for Lagrangian (33), matches the ones originally proposed in Ref. 30, we can consider these results as a rigorous proof of the ones obtained heuristically in the previous paper.

IV. A FULLY POLARIZABLE QM/AMOEBA/DDCOSMO MODEL

In this section, we use the Lagrangian in Eq. (27) to derive the working equations for a coupled QM/AMOEBA/ddCOSMO model. We then show, as a subcase, the coupling of the variational MMPol model with ddCOSMO. A schematic representation of the QM/AMOEBA/ddCOSMO three-layered multiscale strategy is given in Fig. 1. A discussion of the standalone AMOEBA and ddCOSMO is given in the supplementary material; here, we limit the discussion to the coupled scheme, recalling just the necessary equations from the standalone models.

AMOEBA³⁵ is an advanced polarizable force field whose energy functional accounts for bonded interactions for dispersion–repulsion interactions through a 7–14 functional for nonbonded electrostatic interactions through an accurate parameterization.³⁵ Each classical atom is endowed of a set of fixed multipoles (charge, dipole, and quadrupole) M and an isotropic polarizability. In this work, we do not discuss contributions beyond the electrostatic and polarization ones, as they are simple additional contributions to the total energy, which can be added *a posteriori* and are particularly relevant only for the total forces. The total polarization and electrostatic energy, in the presence of a QM density,⁵⁸ can be written as

$$\mathcal{E}^{ele/pol} = \mathcal{E}^{self}(M) + \langle q, V(\rho) \rangle - \langle \mu_s, E(\rho) \rangle + \langle \Theta, G(\rho) \rangle - \frac{1}{2}\langle \mu_d, E_p(M) + E(\rho) \rangle. \quad (34)$$

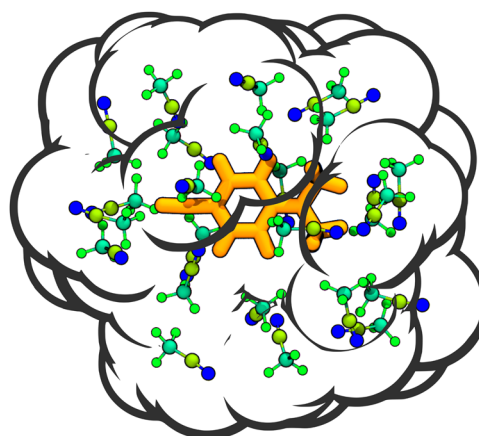


FIG. 1. Representation of the QM/AMOEBA/ddCOSMO approach. The QM molecule is represented in bold orange, the AMOEBA atoms are represented in a color scale of the color depending on the fixed charge [yellow (positive) and blue (negative)], and the ddCOSMO cavity is drawn schematically with dark gray lines.

Here, the first term is the self-interaction of the fixed multipoles, the three following terms are the interactions between the fixed multipoles and the QM density, and the last term is the polarization energy. q , μ_s , Θ , and μ_d are, respectively, the collections of charges, fixed dipoles, quadrupoles, and induced dipoles. The dipoles are computed according to

$$T\mu_d = E_d(M) + E(\rho), \quad (35)$$

where the right-hand side is the inducing field and T is the damped dipole-dipole interaction matrix.⁵⁰ A peculiarity of the AMOEBA force field is that the dipoles are computed according to a field E_d , which is different from the field with which they interact E_p . The two fields are different since they are computed according to two different exclusion rules to avoid overpolarization. In other words, AMOEBA is a quasi-variational model, with $\Theta = E_d$ and $\Psi = E_p$. In order to write the AMOEBA Lagrangian, an additional condition has to be enforced through a set of Lagrange multipliers μ_p ,

$$\begin{aligned} \mathcal{L}(\mu_p, \mu_d) = & \mathcal{E}^{\text{self}} + \langle q, V(\rho) \rangle - \langle \mu_s, E(\rho) \rangle + \langle \Theta, G(\rho) \rangle \\ & - \frac{1}{2} \langle \mu_d, E_p(M) + E(\rho) \rangle \\ & + \frac{1}{2} \langle \mu_p, T\mu_d - E_d(M) - E(\rho) \rangle. \end{aligned} \quad (36)$$

The Lagrange multipliers are obtained by imposing the stationarity with respect to μ_d ,

$$T\mu_p = E_p(M) + E(\rho). \quad (37)$$

An extensive discussion about ddCOSMO can be found elsewhere,^{36,41,60,61} and an introduction is provided in the [supplementary material](#). Briefly, given the solute's potential at the cavity Φ , ddCOSMO solves a linear system to find the reaction potential at the cavity X . Then, the latter can be used to compute the solvation energy. The linear system reads

$$LX = -\Phi, \quad (38)$$

where each quantity is discretized over the spheres i and over the spherical harmonic indices ℓ and m . The energy is written as the scalar product between a function of the solute density Ψ and the reaction field at the cavity X ,

$$\mathcal{E}^{\text{sol}} = \frac{1}{2} \langle \Psi(\rho_{\text{sol}}), X \rangle. \quad (39)$$

Again, this expression is not variational because (i) L is not symmetric and (ii) Ψ and Φ are different functions. A Lagrangian can be easily built according to Sec. II B by introducing a set of Lagrange multipliers S ,

$$\mathcal{L}(X, S) = \frac{1}{2} \langle \Psi, X \rangle + \frac{1}{2} \langle S, LX + \Phi \rangle. \quad (40)$$

The Lagrange multipliers are obtained by imposing the stationarity of Eq. (40) with respect to X ,

$$L^\dagger S = -\Psi. \quad (41)$$

Note that the RHS of this last equation has the opposite sign with respect to the ddCOSMO/ddPCM literature. However, in the following discussion, we prefer to keep Eqs. (40) and (41) in this way

so that the coupled AMOEBA/ddCOSMO linear system can be written in the same form of Eqs. (28) and (29).

The first step to derive the working equations for a QM/AMOEBA/ddCOSMO scheme is to build the complete Lagrangian as in Eq. (27). Here, it is expressed using the notation presented for AMOEBA and ddCOSMO,

$$\begin{aligned} \mathcal{L}^{\text{pol}} = & \mathcal{E}^{\text{self}} + \langle q, V(\rho) \rangle - \langle \mu_s, E(\rho) \rangle + \langle \Theta, G(\rho) \rangle + \frac{1}{2} \langle \mu_d, E(\rho) + E_p(M) \rangle \\ & + \frac{1}{4} \langle X_p + X_d, \Psi(\rho) + \Psi(M) \rangle + \frac{1}{4} (\langle X_p, \Omega \mu_d \rangle + \langle X_d, \Omega \mu_p \rangle) \\ & + \frac{1}{2} \langle \mu_p, T\mu_d - E(\rho) - E_d(M) \rangle + \frac{1}{4} \langle S_p, LX_d + \Phi(\rho) \\ & + \Phi(M) + \Xi \mu_d \rangle + \frac{1}{4} \langle S_d, LX_p + \Phi(\rho) + \Phi(M) + \Xi \mu_p \rangle. \end{aligned} \quad (42)$$

It is important to note that both the MM and QM atoms are the solute in the ddCOSMO model, so the ddCOSMO quantities will belong to a vector space of size (total number of atoms) $\times (\ell_{\text{max}} + 1)^2$, where ℓ_{max} is a parameter decided by the user, and the AMOEBA quantities will belong to a vector space of size (number of AMOEBA atoms) $\times N$, where $N = 1$ for charge and potential arrays, $N = 3$ for dipole and field arrays, and $N = 6$ for quadrupoles and field gradient arrays. The new quantities, not present in the standalone models, are the coupling matrices Ω and Ξ , as well as the functions Ψ and Φ applied to the fixed multipolar distribution M . We describe here the main characteristics of Eq. (42), leaving the cumbersome details to the [supplementary material](#). First, applying the matrices Ω and Ξ to a dipole array μ is equivalent to computing $\Psi(\mu)$ and $-\Phi(\mu)$, respectively, so it is a special case of the computation of $\Psi(M)$ and $\Phi(M)$. Second, the coupling terms are linear functions in M , so they can be written as matrix-vector products. Third, the coupling matrices are rectangular since they send AMOEBA quantities into ddCOSMO quantities and vice versa if transposed.

The equations that determine the polarizations are obtained by imposing the stationarity of Lagrangian (42) with respect to all the degrees of freedom. By imposing the stationarity with respect to μ_d , X_d , and S_d , we get three coupled linear equations that can be written as

$$\begin{pmatrix} T & \Omega^\dagger & \Xi^\dagger \\ \Omega & 0 & 2L^\dagger \\ \Xi & 2L & 0 \end{pmatrix} \begin{pmatrix} \mu_d \\ X_d \\ S_d \end{pmatrix} = \begin{pmatrix} E(\rho) + E_d(M) \\ -\Psi(\rho) - \Psi(M) \\ -\Phi(\rho) - \Phi(M) \end{pmatrix}. \quad (43)$$

By imposing the stationarity with respect to μ_p , X_p , and S_p , the second set of equations is obtained,

$$\begin{pmatrix} T & \Omega^\dagger & \Xi^\dagger \\ \Omega & 0 & 2L^\dagger \\ \Xi & 2L & 0 \end{pmatrix} \begin{pmatrix} \mu_p \\ X_p \\ S_p \end{pmatrix} = \begin{pmatrix} E(\rho) + E_p(M) \\ -\Psi(\rho) - \Psi(M) \\ -\Phi(\rho) - \Phi(M) \end{pmatrix}. \quad (44)$$

Once the linear systems in Eqs. (43) and (44) are solved, the polarizations are fully determined and can be used to compute the energy and properties. We first discuss the computation of the Fock matrix leaving the discussion of energy to Sec. IV A. The Fock matrix is obtained by differentiation of Lagrangian (42) with respect to the density matrix P . For the element $\mu\nu$, the Fock matrix reads

$$F_{\mu\nu} = \langle q, V_{\mu\nu} \rangle - \langle \mu_s, E_{\mu\nu} \rangle + \langle \Theta, G_{\mu\nu} \rangle - \frac{1}{4} \langle \mu_d + \mu_p, E_{\mu\nu} \rangle + \frac{1}{4} \langle X_p + X_d, \Psi_{\mu\nu} \rangle + \frac{1}{4} \langle S_p + S_d, \Phi_{\mu\nu} \rangle. \quad (45)$$

A. Expression for the energy

At the stationary point, the terms of Lagrangian (42) corresponding to the two ddCOSMO constraints vanish. One gets, therefore, the following expression for the polarization energy:

$$\begin{aligned} \mathcal{E} = & \mathcal{E}^{\text{self}}(M) + \langle q, V(\rho) \rangle - \langle \mu_s, E(\rho) \rangle + \langle \Theta, G(\rho) \rangle \\ & - \frac{1}{2} \langle \mu_d, E(\rho) + E_p(M) \rangle + \frac{1}{4} (\langle X_p, \Psi(\rho) + \Psi(M) + \Omega\mu_d \rangle \\ & + \langle X_d, \Psi(\rho) + \Psi(M) + \Omega\mu_p \rangle) + \frac{1}{2} \langle \mu_p, T\mu_d - E(\rho) - E_d(M) \rangle. \end{aligned} \quad (46)$$

In order to evaluate Eq. (46), an expensive matrix–vector product ($T\mu_d$) has to be computed. It is possible to obtain a simpler expression that can be evaluated more efficiently by using some intermediate quantities that are available during the iterative solution to the coupled polarization equations. We report in Algorithm 1 a possible iterative strategy, where we use a macro/micro iteration scheme to solve the coupled linear systems. The macroiteration is done on the AMOEBA degrees of freedom (μ_d and μ_p), and at each macroiteration, we solve iteratively (microiterations) for the ddCOSMO degrees of freedom (X_d , S_d , X_p , and S_p). Using such a strategy, we can avoid the computation of the $T\mu_d$ matrix vector product in the last term by noting that

$$T\mu_d - E(\rho) - E_d(M) = -\Omega X_d - \Xi S_d. \quad (47)$$

As ΩX_d and ΞS_d are available from the iterative solver, we can rewrite the expression for the energy as

$$\begin{aligned} \mathcal{E} = & \mathcal{E}^{\text{self}}(M) + \langle q, V(\rho) \rangle - \langle \mu_s, E(\rho) \rangle + \langle \Theta, G(\rho) \rangle \\ & - \frac{1}{2} \langle \mu_d, E(\rho) + E_p(M) \rangle + \frac{1}{4} (\langle X_p, \Psi(\rho) + \Psi(M) + \Omega\mu_d \rangle \\ & + \langle X_d, \Psi(\rho) + \Psi(M) + \Omega\mu_p \rangle) - \frac{1}{2} \langle \mu_p, \Omega X_d + \Xi S_d \rangle. \end{aligned} \quad (48)$$

ALGORITHM 1. Macro/micro iteration scheme for coupled AMOEBA/ddCOSMO.

- 1: while μ_p, μ_d not converged do
- 2: Compute $\Xi\mu_d, \Xi\mu_p$
- 3: Compute $\Omega\mu_d, \Omega\mu_p$
- 4: Solve direct ddCOSMO: $LX_d = -\Phi - \Xi\mu_d, LX_p = -\Phi - \Xi\mu_p$
- 5: Solve adjoint ddCOSMO: $L^\dagger S_d = -\Psi - \Omega\mu_d, L^\dagger S_p = -\Psi - \Omega\mu_p$
- 6: Compute $\Omega^\dagger X_d, \Omega^\dagger X_p$
- 7: Compute $\Xi^\dagger S_d, \Xi^\dagger S_p$
- 8: Assemble AMOEBA RHS: $E_d - \Omega X_d - \Xi S_d, E_p - \Omega X_p - \Xi S_p$
- 9: Do a Jacobi iteration on the μ_d, μ_p dipoles
- 10: Check for convergence on μ_d, μ_p

B. A special case: A variational-non-variational formulation

A special case of the AMOEBA/ddCOSMO coupling just presented is obtained by replacing the AMOEBA force field with a variational one, such as Wang's polarizable Amber-like force field.⁶² The coupling of such a scheme, called MMPol,⁵¹ with either the polarizable continuum model or ddCOSMO has already been reported in the literature.^{27,55} Here, we consider the coupling of MMPol with ddCOSMO and compare it with the AMOEBA/ddCOSMO coupled embedding model. The differences are few: (i) the energy of the atomistic model is defined in such a way that it is variational and (ii) each classical atom bears only a charge and an isotropic polarizability. According to Sec. III B, the Lagrangian takes the form

$$\begin{aligned} \mathcal{L}(\mu, X, S) = & \mathcal{E}^{\text{self}}(q) + \langle q, V(\rho) \rangle - \langle \mu, E(\rho) + E(q) \rangle + \frac{1}{2} \langle \mu, T\mu \rangle \\ & + \frac{1}{2} \langle X, \Omega\mu \rangle + \frac{1}{2} \langle X, \Psi(\rho) + \Psi(q) \rangle \\ & + \frac{1}{2} \langle S, LX + \Phi(\rho) + \Psi(q) + \Xi\mu \rangle. \end{aligned} \quad (49)$$

By imposing the stationarity, we get

$$\begin{pmatrix} T & \Omega^\dagger & \Xi^\dagger \\ \Omega & 0 & 2L^\dagger \\ \Xi & 2L & 0 \end{pmatrix} \begin{pmatrix} \mu \\ X \\ S \end{pmatrix} = \begin{pmatrix} E(\rho) + E(q) \\ -\Psi(\rho) - \Psi(q) \\ -\Phi(\rho) - \Phi(q) \end{pmatrix}. \quad (50)$$

The expressions for the coupling matrices and for $\Psi(q)$ and $\Phi(q)$ are a special case of those reported for AMOEBA in the supplementary material, as, in this case, the induced dipoles are analogous to the AMOEBA ones and the fixed multipoles are restricted to charges only.

V. CONCLUSIONS AND PERSPECTIVES

In this contribution, we presented a general formalism to treat polarizable electrostatics for both atomistic and continuum models in the context of multiscale QM/classical calculations. The formalism can be used for both variational and non-variational models, and the two formulations have been shown to be consistent, i.e., the variational case can be obtained systematically as a subcase of the non-variational one. We then discussed in a general fashion the coupling between polarizable models by introducing a general set of coupling rules in terms of interaction energy (for variational models) or modified right-hand sides for the polarization equations (for non-variational ones). We used these hypotheses to derive the coupled polarization energy and equations for all possible combinations of variational and non-variational models. In order to show the possibilities of the formalism, we showed that deriving the coupled equations for either a variational and a non-variational (MMPol and ddCOSMO) or even two non-variational models (AMOEBA and ddCOSMO) becomes an easy exercise, which includes the derivation of the coupling with a self-consistent field quantum mechanical treatment.

We hope that this general formalism will be helpful to the community of developers of polarizable models, both in the context of multiscale QM/classical schemes and in one of the purely classical

742 simulations, allowing to easily derive the polarization equations for
743 new models or to couple new and existing models for the first
time.

744 SUPPLEMENTARY MATERIAL

745 See the [supplementary material](#) for more information on
746 AMOEBA and ddCOSMO and their implementation and for the
747 explicit expression of the AMOEBA/ddCOSMO coupling terms.

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754 DATA AVAILABILITY

755 Data sharing is not applicable to this article as no new data were
756 created or analyzed in this study.

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