# Perspective: Polarizable continuum models for quantum-mechanical descriptions

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Polarizable continuum solvation models are nowadays the most popular approach to describe solvent effects in the context of quantum mechanical calculations. Unexpectedly, despite their widespread use in all branches of quantum chemistry and beyond, important aspects of both their theoretical formulation and numerical implementation are still not completely understood. In particular, in this perspective we focus on the numerical issues of their implementation when applied to large systems and on the theoretical framework needed to treat time dependent problems and excited states or to deal with electronic correlation. Possible extensions beyond a purely electrostatic model and generalizations to environments beyond common solvents are also critically presented and discussed. Finally, some possible new theoretical approaches and numerical strategies are suggested to overcome the obstacles which still prevent a full exploitation of these models. *Published by AIP Publishing.* [http://dx.doi.org/10.1063/1.4947236]

## I. INTRODUCTION

Continuum solvation models (CSMs) have a very long history in the prediction of solvent effects and solvation free energies of molecular solutes.[1–3] However only when they have been combined with a quantum-mechanical description of the solute have their applications really exploded in many different fields going from chemistry to biology and to materials science.[4–6] Nowadays, Quantum Mechanics (QM) based continuum models are so popular that at least a version of them is available in any software for electronic structure calculations. Differently to what has happened for classical applications in molecular biology, where continuum models based on the Poisson-Boltzmann equation or the generalized Born approach are prevalent,[7–9] the formulations which have been mostly successful within the QM framework are those introducing a cavity of molecular shape and projecting the dielectric response on the surface of such a cavity. This family of models can be somehow related to two main formulations known as Polarizable Continuum Model (PCM) and Conductor-like Screening Model (COSMO). PCM, originally formulated in 1981 by Miertus *et al.*,[10] during the years has been largely reformulated by different groups. These reformulations have dealt with the theory (as they have involved completely new theoretical models) and the numerical implementation to make the model computationally more effective and/or compatible with different software.[11] Also COSMO, originally formulated in 1993 by Klamt and Schuurmann,[12] has been reformulated various times but in this case the proposed revisions have mostly been of numerical type, e.g., to improve its computational performance and/or to make it feasible in different electronic structure packages. It is worth noting that COSMO has been successively combined with the

statistical thermodynamics treatment of interacting surfaces, which has led to the COSMO for real solvents (COSMO-RS) approach now largely used in chemical engineering.[13] The enormous success that PCM and COSMO have achieved can be surely related to three unique characteristics that they possess, namely, (i) the extreme easiness of use; (ii) the high versatility towards very different molecular solutes (neutral or charged); and (iii) the high quality/cost ratio. All these characteristics come from the assumptions at the basis of the model. The first and most important one says that the atomistic nature of the solvent can be neglected and a dielectric medium can be used instead. The second assumption implies that the linear response (LR) approximation is sufficient to describe the dielectric polarization; as a result the following Poisson's equation applies:

$$-\boldsymbol{\nabla} \cdot \left[ \varepsilon(\mathbf{r}) \boldsymbol{\nabla} \Phi^{\text{tot}}(\mathbf{r}) \right] = 4\pi\rho(\mathbf{r}), \tag{1}$$

where $\Phi^{\text{tot}}(\mathbf{r})$ is the electrostatic potential that has contributions from both the solute (here represented by the charge distribution $\rho(\mathbf{r})$) and the surrounding medium. If finally the dielectric is assumed to be isotropic and homogeneous, the dielectric function $\varepsilon(\mathbf{r})$ can be simplified into

$$\varepsilon(\mathbf{r}) = \begin{cases} 1, & \mathbf{r} \in \text{cavity} \\ \varepsilon_s, & \mathbf{r} \notin \text{cavity}. \end{cases} \tag{2}$$

As a result the only parameters we need are the dielectric constant $\varepsilon_s$ which represents the solvent and the molecular cavity in which the solute is embedded. Within this framework, the most effective way to solve electrostatic problem (1) is to write the total potential $\Phi^{\text{tot}}(\mathbf{r})$ as a sum of two terms: the electrostatic potential produced by the solute's charge density *in vacuo* $\Phi^\rho$ and a *reaction* potential $W^\sigma$, which is only due to the presence of the continuum. The latter is then represented as the potential generated by an apparent surface charge (ASC)

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distribution $\sigma$ on the boundary $\Gamma$ of the molecular cavity,

$$\Phi^{tot}(\mathbf{r}) = \Phi^\rho(\mathbf{r}) + W^\sigma(\mathbf{r}) = \int_{\mathbb{R}^3} d\mathbf{r}' \frac{\rho(\mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|} + \int_\Gamma d\mathbf{s} \frac{\sigma(\mathbf{s})}{|\mathbf{r} - \mathbf{s}|}. \tag{3}$$

$\sigma(\mathbf{s})$ is differently computed in the various formulations of PCM and COSMO; in all cases, however, it is obtained from the two parameters of the model (the dielectric constant and the cavity) and from some electrostatic properties of the solute (the electrostatic potential or the electric field) at the surface. Once $\sigma(\mathbf{s})$ is known, $W^\sigma(\mathbf{r})$ is easily calculated and the problem is completely solved. Notice that the integral representation in Eq. (3) is exact only if the solute's charge density is entirely supported inside the cavity: this is clearly not the case for the electronic charge distribution. Such a limit of the model is known since the very first formulations of CSMs and many numerical strategies have been proposed to correct the so-called "escaped charge" error. It is however important to say that such an error is no longer an issue in modern formulations of CSMs as their definition of the ASC also accounts for the electrostatic potential arising from the escaped charge.[14,15]

Another aspect not to be forgotten to better understand the reasons for the enormous success of CSMs within QM formulations is that their original implementation was very easy as generally limited to single point calculations on small molecular solutes within a Self-Consistent-Field (SCF) QM approach. Only when the CSMs have been generalized to molecular response properties as well as having been extended to larger systems and/or post-SCF descriptions, new and more challenging theoretical and numerical issues have appeared. In parallel, if dielectric functions, going beyond approximation (2), want to be used to describe more complex environments such as interfaces, membranes, and nanoparticles, important revisions of the electrostatic model are required. For all these extensions to be feasible within the same theoretical formalism, a much better combination of numerical accuracy and computational robustness and efficiency is required with respect to the original formulation of the models. These new requirements have led to many reformulations and still today many new developments are in progress. The goal of this perspective is exactly that of presenting the three main lines along which we can expect the most important advances in the near future.

## II. TOWARDS VERY LARGE SOLUTES

To have a more general presentation, it is convenient to introduce a variational formulation of CSMs. Within this framework the electrostatic problem can be reformulated as the search for a minimum of a variational free energy functional $\mathcal{G}(\sigma)$. Its *unique* minimum gives in fact the solvation free energy and its *unique* minimizer is the ASC distribution $\sigma$. The general form of such a functional is[16]

$$\mathcal{G}(\sigma) = \frac{1}{2} \int_\Gamma d\mathbf{s}\,\sigma(\mathbf{s})[\hat{X}\sigma](\mathbf{s}) + \int_\Gamma d\mathbf{s}\,\sigma(\mathbf{s})\Phi^\rho(\mathbf{s}), \tag{4}$$

where $\Phi^\rho$ is the solute's potential *in vacuo*, $\hat{X} = \hat{R}^{-1}\hat{T}$ a self-adjoint, positive integral operator on $L^2(\Gamma)$,[17] and the definitions of the integral operators $\hat{R}$ and $\hat{T}$ depend on the specific continuum model.[12,18,19] Imposing the stationarity of the functional in Eq. (4) one obtains an integral equation for $\sigma$,

$$\hat{T}\sigma = -\hat{R}\Phi^\rho. \tag{5}$$

The solvation free energy is then obtained by inserting the solution $\bar{\sigma}$ to Eq. (5) into the functional in Eq. (4),

$$E_s = \frac{1}{2} \int_\Gamma d\mathbf{s}\,\bar{\sigma}(\mathbf{s})\Phi^\rho(\mathbf{s}). \tag{6}$$

Integral equation (5) can be solved analytically only for the simplest molecular cavities, such as spherical cavities: a numerical method is needed for the general case. The first method historically used to solve the integral equations is the Boundary Element Method (BEM), using a piecewise constant approximation. In particular, the cavity surface is meshed into surface elements (the so-called *tesserae*) and the ASC is assumed to be constant on each tessera. A discretization of the ASC is obtained by imposing that the integral equation holds at a set of *collocation* points, usually the centers of the tesserae, which gives rise to a linear system of the form

$$\mathbf{Tq} = -\mathbf{RV}, \tag{7}$$

where the matrices $\mathbf{T}$ and $\mathbf{R}$ depend on the specific model, $\mathbf{V}$ is the solute's potential (or some other electrostatic property used in the model) evaluated at the collocation points, and $\mathbf{q}$ is a vector that collects the expansion coefficients of the ASC in the piecewise constant basis. The linear system in Eq. (7) is then solved, usually by dense linear algebra techniques such as the LU or Cholesky decomposition.[20] During the years, different meshes have been proposed starting from the one defined by parallels and meridians employed in the original version of PCM.[10] Among the most popular ones, it is worth citing here the GePol algorithm[21] which is still in use in different implementations of PCM and COSMO: the cavity is defined in terms of interlocking spheres (generally centered on the solute's atoms) and each sphere is individually segmented by using the triangular faces of an inscribed regular polyhedron with the desired number of faces (those segments which are partially/fully inside an intersecting sphere are further partitioned/discarded).

The BEM discretization suffers from two major shortcomings: it is not fully suitable to be used for geometry optimizations or molecular dynamics simulations and is computationally very demanding for large solutes. The first point is easily understood by thinking about what happens when, due to a change in the solute's geometry, the number of surface elements changes or two collocation points get very close because of changes in the cavity which is anchored on the solute atoms. In such cases, the energy will be discontinuous and the energy gradients not defined. As a practical consequence, geometry optimizations will struggle to converge and molecular dynamics simulations will exhibit a very poor energy conservation. In 1999, York and Karplus[22] presented the first smooth discretization for the COSMO, addressing such a problem. They achieved this by expanding the ASC in spherical

Gaussians and by using a switching function that weighs the expansion coefficients with a factor that goes from one (fully exposed point) to zero (fully buried point) smoothly whenever a collocation point becomes buried or exposed. The idea of York and Karplus has been extended independently by Scalmani and Frisch[23] (continuous surface charge discretization) and by Herbert and Lange[24,25] (switching-Gaussian discretization) to the PCM. These new discretizations successfully provide for a smooth solvation free energy as a function of the nuclear coordinates; however, they introduce many parameters and, for PCM, do not provide a faithful representation of the integral operators, which, in their discretized counterparts, do not satisfy the same commutation rules as the corresponding continuous integral operators.[26]

The second problem concerns the computational cost associated with solving the PCM or COSMO equations when dealing with large solutes. Both the BEM and Gaussian-based discretizations give rise to very ill-conditioned,[17] large linear systems which require a large computational effort to be solved even when iterative techniques are used,[20,27] due to the large number of matrix-vector products required. An important improvement on this side was introduced by Scalmani and co-workers,[28] who used the Fast Multipole Method[29] (FMM) to perform the matrix-vector products with a computational cost scaling linearly with the size of the system. Unfortunately, PCM is a very difficult problem for the FMM,[30] as it requires the evaluation of potentials at a very large number of densely packed points, requiring therefore conservative choices for the multipolar expansions in order to retain enough numerical precision to converge the linear equations. Furthermore, the use of the FMM does not solve the bad conditioning problem.

Recently, a new numerical paradigm based on Schwarz's domain decomposition method has been proposed for the COSMO by Cancès and co-workers.[31] Such a new discretization, known as domain-decomposition (dd) COSMO, allows for smooth energy surfaces, and for computational costs and memory requirements that are intrinsically linear with respect to the size of the system and overall much smaller than in previous implementations. Furthermore, the ddCOSMO linear system is well conditioned (convergence is usually observed after 20–25 iterations) and the ddCOSMO solver can easily be parallelized.[31,32] ddCOSMO has been implemented for both quantum mechanical[33,34] and classical solutes[35] and a stand-alone implementation is freely available.[36] An extension of the domain decomposition formalism to the PCM has also been recently proposed.[37]

Although ddCOSMO represents a major computational improvement with respect to the previous implementations, as it combines the smoothness of Gaussian-based discretizations with an extremely high computational efficiency, it is still a very recent method which needs further improvements and developments before it can be considered mature. In particular, we have the following:

- Only energy, gradients, and electric properties have been implemented: an extension is needed in order to be able to compute magnetic, chiral, and vibrational properties. The latter task requires the implementation of analytical second derivatives of the ddCOSMO

solvation energy with respect to the positions of the nuclei, which is *per se* a quite formidable task.

- ddCOSMO has been interfaced with classical (including polarizable), semiempirical, and QM levels of theory; however, only SCF-based (i.e., Hartree-Fock (HF) and Density Functional Theory (DFT)) models are available at the moment.

- The generalization to the dielectric model (ddPCM) is, at the moment, at a very early stage of development. There only exists a pilot implementation for the energy of a classical solute, which still involves a computational step that scales quadratically with the size of the system. A fully linear scaling implementation, the implementation of analytical gradients, and the interface with a QM level of theory for the solute are mandatory steps before ddPCM can be considered for applications.

We conclude this section with a general remark, which applies both to Gaussian and domain decomposition based discretizations: both are in fact implemented for van der Waals cavities, i.e., cavities obtained as the interlocking of van der Waals spheres centered on each solute's atom. The extension of CSMs to very large systems requires us to go beyond this description,[6] as van der Waals cavities can become extremely complex in their topology when the number of atoms largely increases and they tend to have holes and pockets that allow the solvent to penetrate in unphysical regions (see Figure 1). The implementation of CSMs for more general cavities, such as the so-called solvent excluded surface, is challenging in particular when analytical derivatives are required, because of the difficulties in finding a regular parametrization of such surfaces. However, this is necessary in order to address a physical shortcoming of the present implementations. A completely alternative strategy would be that of using isodensity surfaces. This has been attempted some years ago[38] but at that time the implementation of the continuum model was still not efficient enough. Reconsidering this strategy now is probably worth it even if the issue of analytical derivatives is even more challenging here.

## III. FROM STATIC TO TIME-DEPENDENT (TD) QM DESCRIPTIONS

Despite their long and successful history, the coupling between CSMs and QM models is fully understood, in the sense that a universal agreement on its definition and implementation exists, only for self-consistent field (SCF) descriptions, such as Hartree Fock (HF), Density Functional Theory (DFT), or multi-configurational SCF. Other methodologies, including post-HF treatments and linear response based descriptions of excited states, such as time-dependent (TD) DFT, still represent a more open theoretical problem and a general, common formalism to define the coupling does not exist yet.

This difficulty is due to the fact that the CSM introduces a density dependent term in the solute's Hamiltonian,

$$\hat{H}^{eff} = \hat{H}^0 + \hat{V}_\sigma = \hat{H}^0 + \sum_i q_i(\rho)\hat{V}_i, \qquad (8)$$
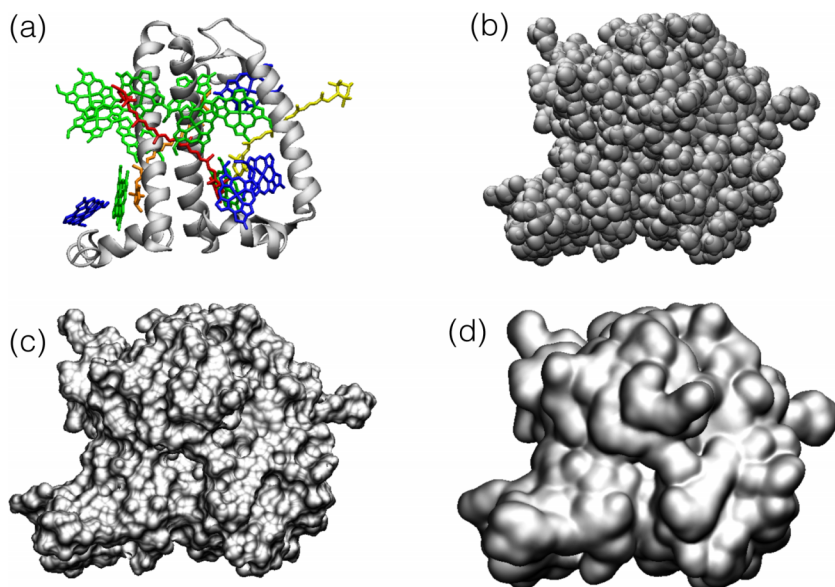
FIG. 1. (a) Crystal structure of a pigment-protein light-harvesting complex (CP29) present in photosystems II of plants: in green are reported the chlorophylls a, in blue the chlorophylls b, and in red, orange, and yellow the three carotenoids. For clarity, the chlorophyll phytyl chains are not shown. (b) The van der Waals cavity obtained scaling each radius by 1.2. (c) Solvent excluded surface obtained for a probe radius of 1.3. (d) Isodensity surface extracted from a volumetric Gaussian density map with density isovalue of 0.5. All the surfaces have been generated with Visual Molecular Dynamics (VMD) software.[39]

where $\hat{H}^0$ is the Hamiltonian of the isolated QM molecule, $q_i$ are the ASCs, and $\hat{V}_i$ is the electrostatic potential operator at the ASC collocation points.

As a result, a non-linear Schrödinger equation needs to be solved. This is not a problem for SCF models, as an iterative procedure involving density dependent operators is employed by default, but it makes the coupling with methods that define the solute's wavefunction and energy by computing a set of amplitudes not straightforward. Three different schemes of the coupling have been proposed originally in the context of many-body perturbation theory[40,41] and then generalized to other post-HF methods.[42–46] The first, known as Perturbation to Energy (PTE), solves the SCF/CSM problem and then uses the orbitals to assemble or compute the amplitudes without modifying the equations. The second, known as Perturbation to density (PTD), computes a post-HF one-body density matrix *in vacuo* and uses it to compute the solvation energy. Both schemes neglect the coupling between solvation and electronic correlation. The third scheme, known as Perturbation to Energy and Density (PTED), can be thought as the iterative combination of PTE and PTD, where the PTE relaxed density is used to update the CSM operator, which is used to solve a new set of QM equations until self-consistency is reached. PTED implementations where the HF solution is recomputed with an updated operator[47] or where only the post-HF equations are solved again[48,49] exist. It should be noted that, although the PTED model seems most physically complete, it introduces spurious terms in a perturbative energy expansion.[50]

A similar manifold of implementations and coupling definitions exists in time-dependent (TD)-SCF formulations for describing the solvent effects on excitation processes. The most common one, known as linear response (LR) CSM formulation, computes the response of the solvent to a transition density and does not include any state specific (SS) effect. Such a formulation is the default coupling of CSMs with TDHF, CIS, and TDDFT formulations. While its consistency with linear response theories is clear, its physical meaning has been interpreted in different ways.[51,52] A detailed analysis has been presented by using two interacting systems having two levels each and representing the solute and the solvent, respectively.[53] Within this picture, the LR-CSM term has been interpreted as a component of the solute-solvent dispersion interactions: the oscillating transition density of the solute induces an oscillating polarization in the solvent which creates an in-phase reaction field which interacts back with the transition density. The LR-CSM formulation has been shown to properly describe the solvent (nonequilibrium) effect in excitations involving bright states characterized by a large transition dipole moment. The LR-CSM formulation, however, lacks the capability of describing the relaxation of the reaction field with the excited state density: it is therefore not suitable to model excitations involving large changes in the solute's charge distribution such as Charge-Transfer (CT) like excitations. Moreover it cannot be used to get a correct description of the solvent effects upon relaxation of the excited state leading to emission or other photochemical processes.

To overcome this shortcoming, various models have been introduced to recover a state-specific (SS) description of the solvent response. Such formulations inherit their spirit from the PTED implementations for post-HF methods and involve an iterative process, the definition of which depends on the specific model (see Fig. 2). We can identify three main families of SS implementations. The External Iteration (EI) scheme[54] uses the excited state relaxed density to compute a new reaction field, which is added to the Fock operator as an external field and used to compute new orbitals, a new linear response transition energy, a new relaxed density, and so on until self-consistency is achieved. The Vertical Excitation Model (VEM)[55] is a different iterative implementation where the reference ground state is kept unchanged, and only the CSM response contribution is updated using the relaxed density matrix until self-consistency. The first iteration of the VEM corresponds to a perturbative correction to the reaction field which is known as corrected Linear Response (cLR) scheme.[56]

Unfortunately, it is difficult to find a non-heuristic justification when one has to choose among such a large
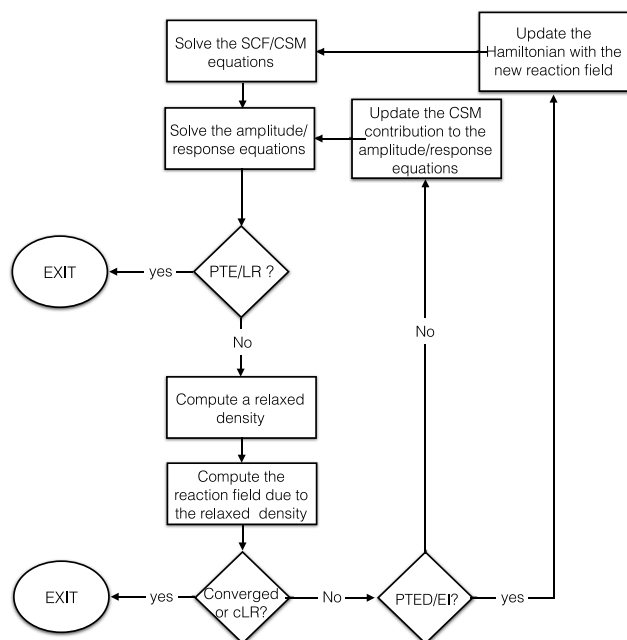
FIG. 2. Schematical representation of the pathway followed within each different coupling scheme or SS formulation.

manifold of schemes. At the present stage, only a limited number of theoretically sound analyses have been presented on the problem[49,53,55] and no rigorous, general theoretical framework exists that can be used to better understand the various approximations. All the different schemes have in fact specific weak points. One problem which is common to self-consistent SS models is that the excited state is no longer orthogonal to the equilibrium ground state, which poses an interpretation problem. As it regards, instead, the simplest cLR approach, a strong limit is that it cannot improve the excited state density but only the excitation energies; this however has not impeded the extension of the application of the model, through finite difference approaches, to excited state geometries and properties.[57,58] On the opposite site, altering the SCF orbitals as done in the EI scheme by computing them in the reaction field of the excited state can lead to an unexpected situation. Especially when solvation effects in the excited state are very strong, an EI scheme can introduce a large state contamination, which could move the reference state from the variational minimum and exacerbate solvation effects in an unphysical way. A typical example of such a problematic behavior can be observed when an EI treatment is used to describe CT excited states.[59]

Variational formulations provide, in the opinion of the authors, the most general and sound theoretical tool to address the aforementioned problems. A given level of theory is characterized by a definition of the energy $\mathcal{E}(\mathbf{t})$ (including, for TD-SCF, the transition energies), which will depend on some set of parameters $\mathbf{t}$ that are determined by a set of equations $\mathbf{f}(\mathbf{t}) = 0$ (amplitude equations, linear response equations, etc.). It is possible to formulate such a method equivalently by introducing a Lagrangian energy functional

$$\mathcal{L}(\mathbf{t}, \bar{\mathbf{t}}) = \mathcal{E}(\mathbf{t}) + \bar{\mathbf{t}}^{\dagger}\mathbf{f}(\mathbf{t}), \qquad (9)$$

where $\bar{\mathbf{t}}$ is a set of Lagrange multipliers introduced to enforce the amplitude equations. The stationarity conditions for the functional in Eq. (9) can then be used to define the energy and its derivatives. A global variational functional including the PCM would then be

$$\mathcal{L}^{eff}(\mathbf{t}, \bar{\mathbf{t}}, \sigma) = \mathcal{L}(\mathbf{t}, \bar{\mathbf{t}}) + \mathcal{G}(\sigma, \mathbf{t}, \bar{\mathbf{t}}), \qquad (10)$$

where $\mathcal{G}$ is the functional defined in Eq. (4) and the dependence on the amplitudes and Lagrange multiplier is contained in the coupling term

$$\mathcal{E}_c = \int_{\Gamma} d\mathbf{s}\, \sigma(\mathbf{s})\Phi^{\rho}[\mathbf{t}, \bar{\mathbf{t}}](\mathbf{s}). \qquad (11)$$

A hierarchy of coupling models could then be obtained by imposing the stationarity of the functional with respect to the different parameters (amplitudes, molecular orbitals, etc.) that define the wavefunction or by imposing with the proper Lagrange multipliers the various conditions that the wavefunction has to satisfy, such as the orthogonality of the orbitals, or the fact that such orbitals solve the SCF equations and so on, in the spirit of that proposed, for instance, by Furche and Ahlrichs for TD-DFT gradients.[60] Notice that Furche's approach has also been used in the formulation of TD-DFT/CSM gradients, albeit without introducing the CSM polarization as an independent degree of freedom.[61]

The use of a variational formulation, which introduces the polarization degrees of freedom of CSMs as an independent variable, has another possible outcome: time dependent formulations.[62] The variational CSM energy can serve as a potential energy for the polarization which can be used in an extended Lagrangian formulation to propagate it in time. The interest of time-dependent formulations goes beyond the computational advantages represented by a Car-Parrinello like propagation of the ASCs. Such formulations can be in principle used to study non-equilibrium, time-dependent solvation in a real-time (RT) picture. This framework has been recently explored independently by two groups[63,64] within a RT-TDDFT formulation. The two formulations introduce an equation of motion for the ASC by rewriting Equation (7) in the frequency domain and using the full spectrum of the solvent's frequency-dependent dielectric permittivity $\varepsilon(\omega)$. Fourier transforming the resulting equation back to the time domain, one arrives at the EOM for the ASC as follows:

$$\mathbf{q}(t) = \int_{-\infty}^{t} dt'\, \mathbf{Q}(t - t')\mathbf{V}(t'), \qquad (12)$$

where the time dependent kernel $\mathbf{Q}(t - t')$ which accounts for the (causal) delayed polarization effects is differently defined in the COSMO or PCM formulations of the model.[64]

The time evolution of the solute's electronic degrees of freedom is finally obtained by solving the quantum Liouville equation, which within the TDDFT framework[65] formulated using an orthonormal basis is

$$\dot{\mathbf{P}}(t) = -i[\mathbf{K}(t), \mathbf{P}(t)], \qquad (13)$$

where the Kohn-Sham (KS) matrix $\mathbf{K}(t)$ is a function of the time-dependent electronic density of the system, $\mathbf{P}(t)$, and the time-dependent polarization charges of the dielectric medium $\mathbf{q}(t)$.

The important aspect is that the mutual coupling between the classical evolution of the apparent charges (**q**) and the quantum evolution of the density matrix (**P**($t$)) is, respectively, mediated by the molecular potential **V**(**P**($t$)) in Eq. (12) and by the KS matrix **K**($t$) in Eq. (13), which has a dependence on the apparent charges through the solute-solvent interaction term $\hat{V}_\sigma(t)$.

The applications of this RT approach are not limited to the treatment of nonequilibrium solvation effects but they can be used for the general treatment of electronic dephasing and energy dissipation in electronic dynamics calculations.

## IV. BEYOND THE STANDARD FORMULATION

As shown above, continuum models have been developed to describe solute-solvent electrostatic interactions. However, along their evolution, additional types of interactions, namely, of repulsive and dispersive origin, have been added by semiempirical functional forms. A popular approach to account for these interactions relies on the use of empirical classical pair potentials between solute and solvent atoms. By further assuming a step-like behavior of the solvent distribution the whole effect can be projected on the cavity surface and numerically solved by using the same mesh used for the electrostatic term.[66] An alternative approach is instead based on the use of a linear relationship with the solvent exposed surface.[67]

As CSMs imply the creation of a cavity within the solvent, an additional energy term, the so-called "cavitation energy," is introduced and associated with the work spent in forming the cavity in the absence of solute-solvent interactions. To account for such an energy, the scaled particle theory has been used within the Pierotti-Claverie formulation[68,69] which extends the theory to nonspherical solutes. In other formulations, cavitation and repulsion/dispersion energies are treated together through an effective term proportional to the solvent accessible surface through the surface tension of the solvent.[70]

In all these cases, the nonelectrostatic contributions can only introduce a shift in the energy of the solvated molecule but have no effect on its electronic charge distribution. On the contrary, nonelectrostatic interactions, and particularly dispersion, are expected to significantly affect the electronic charge distribution and play an important role in determining its response properties, especially when the solvent is nonpolar. Recently, nonelectrostatic effects, and in particular dispersion, have gained prominence in the literature of condensed matter processes.[71,72] Different theoretical formulations and computational approaches have been proposed especially within the DFT formalism.[73–75] In many cases, however, the proposed approach has been optimized for finite systems (dimers to clusters) while it is not immediately applicable to a molecule in solution or embedded in a macromolecular matrix. In the latter cases, a continuum formulation of the perturbation could represent an effective option and a real advantage in terms of computational cost. The main problem is that these nonelectrostatic interactions are intrinsically quantum-mechanical: dispersion is a nonlocal electron correlation

effect, whereas repulsion arises from the Pauli exclusion principle. The request of reformulating them within a classical picture as that represented by a continuum model necessarily introduces much greater difficulties than electrostatics. Still, attempts to describe solute-solvent dispersion and repulsion effects through QM/CSM approaches have been proposed. The self-consistent model of Amovilli and Mennucci,[76] developed reformulating the theory of weakly interacting systems within the PCM, is an example of such attempts, together with the model more recently developed by Pomogaeva and Chipman[77] from a density functional formulation of dispersion energy. In the Amovilli-Mennucci formulation, specific repulsion and dispersion operators acting explicitly on the QM solute are introduced. The repulsion term is assumed to be proportional to the so-called "escaped charge," i.e., the solute electronic density which extends beyond the boundaries of the molecular cavity. The expression for the dispersion energy is instead achieved by similarity with electrostatics introducing another ASC density induced on the cavity surface by the solute transition charge densities and depending on a dielectric constant calculated at imaginary frequencies. A completely different formulation has been proposed[78] within the self-consistent continuum solvation (SCCS) model originally developed by Fattebert and Gygi[79] for periodic boundary codes using plane-waves. The approach expresses the sum of dispersion and repulsion energies as a term linearly proportional to the quantum surface and the quantum volume of the molecular cavity defined by the finite difference between two isosurfaces of the electronic density. In all cases, the applications have been mostly limited to the calculation of the energy of molecular solutes in their electronic ground state. Indeed, the investigation of how repulsion and, in particular, dispersion interactions change by moving from a ground state solute to an excited one is extremely interesting. For example, for ground-state species, the dispersion energy is always negative; that is, it corresponds to attraction, although in excited states it may become repulsive.

In Section III we have already commented on the fact that the common LR implementation of CSM has been interpreted as to be part of the dispersion contribution. Recently, attempts to extend the Amovilli-Mennucci formulation of dispersion effects to excitation processes have been presented within a TDDFT formalism.[52,80] The results presented so far show that the role of these interactions is not negligible especially in low polar environments. Similar findings were also obtained by Marenich *et al.*[81] in terms of a Solvation Model with State-Specific Polarizability (SMSSP) for dispersion which introduces a semiclassical formulation based on the spherically averaged dipole polarizability of the solute's molecule (either in its ground or excited electronic state) and the refractive index of the solvent.

In spite of these interesting attempts, a really general formulation to be used self-consistently with the QM description of the solute is still missing. An important step forward has been recently presented by Ferri *et al.*[82] for surfaces by rewriting the pairwise-additive interatomic $C_6 R^{-6}$ term into a functional of the electron density, thus leading to a self-consistent approach which is only minimally empirical. The reformulation of this approach within a continuum

framework is neither straightforward nor well established; however, it seems a very promising direction of development.

Together with the extension to nonelectrostatic interactions, in recent years CSMs have been reformulated to introduce more complex dielectric functions with respect to that reported in Eq. (2). Two main directions have been followed, one considering dielectric media with macroscopic anisotropies and inhomogeneities, and the other allowing the dielectric function to be dependent on the solute electronic density. The latter case has been recently used within the reformulation of the SCCS model,[83] in which the medium is defined in such a way that the interface between the solvent and the cavity hosting the solute is smooth and determined self-consistently by the ground-state electronic charge-density of the latter. This is achieved by defining an effective local dielectric constant such that the dielectric is excluded ($\varepsilon = 1$) from the inner part of the solute, where the electronic density is high, while it smoothly goes to the bulk dielectric constant of the solvent ($\varepsilon = \varepsilon_s$) outside the solute, where the electronic density goes to zero. This formulation is extremely effective when implemented within plane-wave density-functional theory and combined with periodic solid-state systems.[84]

Moving to attempts to go beyond the isotropic and homogeneous limit, a significant step further has been achieved thanks to one of the most extensive reformulations of PCM. This reformulation, known as Integral Equation Formalism PCM (IEFPCM),[18,85] has in fact allowed us to extend the expression of the ASCs reported in Eq. (5) to any dielectric for which the electrostatic equation outside the cavity is linear, with constant coefficients. In fact, one can associate with any linear electrostatic equation, formally denoted by $L_e V = 4\pi\rho$ (where $L_e$ is a differential operator with constant coefficients), a function $G_e(\mathbf{r})$ called the Green's kernel of the operator $L_e$ and defined by

$$L_e G_e = 4\pi\delta_0, \tag{14}$$

where $\delta_0$ is the Dirac distribution. Examples of this general formulation have been presented for anisotropic media for which the dielectric constant becomes a matrix or weak ionic solutions for which the linearized form of the Poisson-Boltzmann equation can be used. Successively the same approach has been used to describe a diffuse interface, defined as a medium with a position-dependent permittivity. In this case, the Green's function can be viewed as a sum of a Coulomb-like term and an image potential term which both depend on the shape of the permittivity across the interface.[86] The latter is usually be expressed as $\varepsilon(z)$, where $z$ is the distance with respect to the interface. This formulation, which has been recently extended to nonelectrostatic effects,[87] represents a valid cheap alternative to MD simulations when one is interested in predicting energies and properties of molecular systems at interfaces and in membranes.[88]

A similar extension has been proposed to describe the effects of plasmonic specimens on the electronic properties of closeby molecules and their response to applied fields. Plasmonic systems, such as metal nanoparticles (MNPs), are in fact becoming increasingly important in spectroscopies and devices because of their ability to enhance, even by several orders of magnitude, the photophysical properties of

neighboring (supra)molecular dyes. The common understanding of the effectiveness of MNPs in optical phenomena is in terms of the so-called localized surface plasmon resonances (LSPRs). These are collective excitations of the electron gas confined in the nanoparticle, which have unusually large transition multipoles and thus are able to enhance the phenomena involving electromagnetic fields. LSPRs can also couple to the electromagnetic fields emitted by molecules placed in the vicinity of the MNP, leading in turn to a strong modification of the radiative and nonradiative properties of the emitter. The basic idea beyond a modelization of MNPs through CSMs is that in the case of electrostatic interactions they behave as a perfect conductor, while for a time-dependent response, they can be considered as a dielectric with a given complex dielectric function. Also in this case the proper Green's function to be used can be defined as the sum of a Coulomb-like term and an image potential term.[89] The main advantage of this formulation is that the apparent charges which represent the response of the nanoparticle(s) are spread on the molecular cavity surface only. This clearly represents an enormous reduction in the computational cost as the dimensionality of the electrostatic problem remains limited to the surface of the cavity containing the QM solute whatever the dimension of the nanoparticle. However, this method requires us to define (either analytically or numerically) the proper Green's function characteristic of the region of space external to the molecular cavity for the chosen system. This is not always possible when nanoparticles of general shapes are used. In those cases, a hybrid strategy has been proposed[90] which reformulates the IEFPCM equations for all the different interfaces present in the system, the surface of the metal body and, in the case of the presence of a solvent, the molecular cavity. For the generation of the metal specimen, an algorithm similar to the one defined for the molecular cavity is used: the metal body is built as the union of interlocking spheres of arbitrary radius and position. Playing with these two parameters and the total number of spheres generated, it is possible to control the exact shape and dimension of the MNP.

Of particular interest is the application of the plasmonic formulation of IEFPCM to simulate plasmonic effects on the absorption and fluorescence of molecular dyes. This has been achieved within the LR scheme described in Section III. In this case the inclusion of the PCM term within the linear-response equations involves also the response of the MNP through its ASCs. Since such a response is determined in terms of a complex dielectric function, the poles of the resulting equations are complex as well. While their real parts represent the excitation energies such as for purely real response functions, their imaginary parts determine the metal-induced nonradiative decay rates. This means that by using a single theoretical framework, we can investigate the plasmonic effects on both radiative and nonradiative processes of nearby dyes. More recently, the same approach has been coupled to a Molecular Mechanics (MM) polarizable embedding to simulate the same processes on the pigment-protein complexes which act as light-harvesting systems in natural photosynthetic organisms.[91,92] We expect that many interesting results will be obtained using this kind of simulations not only to reproduce

and interpret experiments but also to suggest general rules to design novel biohybrid devices with the selected enhanced responses.

## V. CONCLUDING REMARKS

We have presented the state of the art of polarizable continuum solvation models in the context of quantum mechanical calculations. We pointed out how the evolution of computational techniques in quantum chemistry and the widespread use of gradient techniques to perform geometry optimizations and molecular dynamics simulations require the numerical setup of CSM to be rethought and optimized. This is particularly true when solutes of large dimensions or hybrid QM/MM descriptions are considered. The recently introduced domain decomposition based implementation has been presented as an example of strategy which exhibits all the nice required properties to extend the applicability of CSM to large systems. The theoretical background of CSM in quantum chemistry has then been quickly reviewed and the various strategies introduced to couple CSM with post-SCF and excited states QM methods, as well as time dependent formulations, have been presented. This is a challenging field of development for CSMs, as a common agreement on how to define the coupling between the classical and the QM descriptions has not yet been established. Variational formulations are, in our opinion, the key formal tool to tackle these complex problems and to provide a common, rigorous framework. Real time approaches, a new, exciting development recently introduced in the CSM scene, represent a further important challenge in the modeling of non-equilibrium effects and other time-dependent phenomena. The necessity of extending QM-based CSMs beyond the realm of electrostatic interactions has also been pointed out, showing that the attempts presented so far will be soon overcome by more general and efficient formulations. Finally, the unique characteristic of CSMs to be extended to treat environments of increasing complexity still maintaining the same simple theoretical formalism has been underlined: also along this line, new important developments are surely to be expected.

## ACKNOWLEDGMENTS

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