

Self-Consistent Field and Polarizable Continuum Model: A New Strategy of Solution for the Coupled Equations

Filippo Lipparini,^{*,†} Giovanni Scalmani,[‡] Benedetta Mennucci,[§] and Michael J. Frisch[‡]

[†]Scuola Normale Superiore, Piazza dei Cavalieri 7, 56126 Pisa, Italy

[‡]Gaussian, Inc., 340 Quinpiac Street Building 40, Wallingford, Connecticut 06492, United States

[§]Dipartimento di Chimica e Chimica Industriale, Università di Pisa, Via Risorgimento 35, 56126 Pisa, Italy

 Supporting Information

ABSTRACT: We present a new strategy for the solution of the self-consistent field (SCF) equations when solvent effects are included by means of the polarizable continuum model (PCM). By exploiting the recently introduced variational formalism of the PCM (VPCM), we are able to recast the self-consistent reaction field problem as an energy functional of both electronic and polarization degrees of freedom. The variational minimization of such a functional leads to the free energy of the solvated molecule at a given geometry. In this contribution we describe an effective procedure and its implementation to achieve the solution of such a variational problem. Moreover, we present numerical evidence that the new approach is superior to the traditional one in terms of performance, especially when a relatively inexpensive semiempirical method is used to describe medium- and large-size solutes.

1. INTRODUCTION

The solution of the independent particle problem by means of a self-consistent field (SCF) approach is probably the most common type of calculation performed today in the field of computational chemistry. Indeed, while they differ in the definition of the effective one-electron Hamiltonian, methods like Hartree–Fock (HF), the Kohn–Sham (KS) formulation of density functional theory (DFT), and many less accurate and computationally less expensive semiempirical methods^{1–3} share the SCF procedure as the approach to solve the underlying nonlinear eigenvalue equations. Moreover, SCF-level calculations are so widely used because they still represent a good compromise between computational cost and accuracy of the results, while the maximum size of the systems that can be studied using off-the-shelf computers increases steadily with the progress of both hardware and software technologies.

Recent efforts to extend the parametrization of semiempirical methods beyond the second row of the periodic table have been fairly successful and have led to the introduction of the PM6 method.³ These developments have the potential of making semiempirical methods a rather attractive alternative (or complement) to *ab initio* techniques, as they drastically increase the size of the molecular systems that can be approached, while keeping the computational cost manageable and still being able to reproduce nonclassical effects. In fact, despite their use of parametrization, semiempirical methods remain quantum mechanical (QM) in their principles.

The range of applicability of any method involving the SCF procedure has been further extended by their generalization to the treatment of molecules in the condensed phase. Among the models developed to account for the effects of the microscopic environment on molecular structure, properties and processes, the polarizable continuum model^{4–6} (PCM) is one of the most successful, thanks

to its generality and its versatility. According to this model, the solvent is described by means of a structureless polarizable dielectric medium. This leads to a dramatic reduction in the number of degrees of freedom as compared to explicit solvent models, while preserving a sufficiently accurate description of the interaction between solute and solvent. In addition, despite the apparently oversimplistic description of the solvent, the PCM model has been successfully applied, with very limited increase in complexity, to less uniform environments,⁷ such as anisotropic solvents, ionic solutions, interfaces between two different liquids, membranes, etc.

The polarization field (the reaction field) of the dielectric is represented by means of an apparent surface charge (ASC) distribution, located at the boundary between the dielectric medium and an empty cavity hosting the solute molecule (the molecular cavity). Over the years, various strategies have been proposed and discussed that would turn the PCM formal setup into a robust and efficient computational tool.^{8–10} In the most recent formulation, the ASC is represented with a continuous charge distribution,^{11,12} and it is expanded in a basis set of spherical Gaussian functions. The expansion coefficients, which have the physical meaning of surface polarization charges, are obtained as the solution of a linear system of equations whose dimension is given by the number of surface elements used to discretize the surface of the molecular cavity. The right-hand side of the PCM linear system depends on the solute structure and the charge distribution through its electrostatic potentials. In the case of polarizable solutes, i.e., when a QM method is used to describe the solute's density, the overall problem becomes nonlinear, and the optimal (in the variational sense) mutual polarization of both the solute and the solvent must be achieved.

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From the formal point of view, the inclusion of the effect of the environment in the QM description of the solute is not a difficult task, as the SCF nonlinear equations maintain the same structure and the one-electron effective Hamiltonian (the Fock operator) is simply augmented by a term that represents the polarization field. The latter, in turn, is updated at each SCF cycle using the new solute's density and solving the PCM problem to evaluate the ASC. The computational machinery needed to perform an SCF calculation in the gas phase or in solution is substantially the same in the sense that no new integrals or other difficult to compute quantities are required to form the additional solvent response term in the Fock operator.¹²

On the other hand, the relative cost of the solution of the SCF equation in the gas phase and in solution may vary enormously. The cost of solving the PCM equations depends on the number of surface elements used to discretize the solute–solvent interface, and the latter is fixed once the solute geometry is known. However, the cost of computing the gas-phase Fock operator and the few additional quantities involving both solute and solvent (e.g., the solute's electrostatic potential at the surface elements) can vary dramatically depending on the underlying choice of the QM method. The inclusion of solvent effects according to the PCM model adds very little to the overall cost of an accurate DFT calculation on a small or medium system, using a large basis set; on the contrary, when a cheap semiempirical Hamiltonian is used to describe a solute containing several hundred atoms, the cost of PCM quickly becomes the most expensive step. This is a remarkable disadvantage and prevents the application of PCM to study large and complex systems in solution using semiempirical methods, while the same calculations in the gas phase can be performed using very little computational resources.

Recently, a variational formulation of the PCM has been introduced.¹³ In this new scheme, hereafter called VPCM, the polarization charges are not defined as the solution of a linear system of equations but rather as the location within the space of the polarization degrees of freedom where a suitable free energy functional is minimum. In other words, the PCM equations are recast as a minimization problem. A free energy functional is defined which depends on both the structural and electronic degrees of freedom of the solute and on the solvent polarization degrees of freedom. When variationally minimized with respect to all these parameters, the PCM energy functional provides the free energy of the polarized solute at its equilibrium geometry in solution.

There are many application under consideration for the VPCM free energy functional such as: (i) simultaneous optimization of geometry, electronic density, and polarization charges to reduce the overall computational cost of a SCF level calculation; (ii) evaluation of the free energy in solution in the context of post-SCF methods, where the reaction field introduces a coupling among the various quantities that contribute to the one-particle density matrix, without resorting to very expensive iterative procedures;^{14,15} (iii) application of PCM in connection with extended Lagrangian ab initio molecular dynamic methods¹⁶ (e.g., Car–Parrinello¹⁷ or atom-centered density matrix propagation, ADMP).^{18,19}

In ref 13 a scheme to simultaneously optimize both the molecular geometry and the polarization charges has been proposed and applied successfully to solutes described by a molecular mechanics (MM) function. In this contribution, we describe a similar approach for the simultaneous optimization of the solute electronic density and the PCM polarization charges

within the SCF procedure, which we shall use, to maintain consistency, the same VPCM acronym. By defining the proper free energy functional of both the density matrix and the polarization charges and carrying out a variational minimization with respect to both classes of parameters, we show that the functional minimum corresponds to the correct free energy in solution for the chosen form of the one-electron Hamiltonian and for a given solute geometry. Within this scheme it is possible to achieve an optimal partition of computational resources between the calculation of the gas phase and the solvent-related terms in the Fock operator, and we demonstrate that this is particularly important when the cost of the gas-phase terms is small like, e.g., when a semiempirical Hamiltonian is used. In practical terms, we show how to exploit standard direct inversion in the iterative subspace (DIIS)^{20–22} extrapolation techniques, which are commonly used to improve SCF convergence, to accelerate the minimization of the free energy functional with respect to both the density matrix and the PCM polarization charges.

This paper is organized as follows. In Section 2 we shortly recall the basic formalism of the PCM model, both in its standard form and according to the new variational scheme. A free energy functional suitable for the simultaneous solution of the SCF and PCM equations is defined, and the associated working equations are derived. Lastly, the implementation of the coupled minimization algorithm is discussed. In Section 3 we report the results of some illustrative calculations including, in particular, semiempirical single point calculations and geometry optimizations.

2. THEORY

2.1. Formalism. The PCM model solves the Poisson equation in the presence of a dielectric medium outside an empty cavity C which hosts the solute. The surface $\Gamma = \partial C$ is the boundary of this cavity and represents the interface between solute and solvent. The electrostatic potential $\varphi(\mathbf{r})$ is the solution of Poisson's equation:

$$\nabla \cdot [\varepsilon(\mathbf{r}) \nabla \varphi(\mathbf{r})] = -4\pi\rho(\mathbf{r}) \quad (1)$$

where $\rho(\mathbf{r})$ is the (nuclear and electronic) charge density of the solute. The dielectric constant function assumes, for a homogeneous solvent, the simple form:

$$\varepsilon(\mathbf{r}) = \begin{cases} 1 & \mathbf{r} \in C \\ \varepsilon & \mathbf{r} \in C \end{cases} \quad (2)$$

where ε is the macroscopic dielectric permittivity of the solvent. Using eq 2 and the appropriate boundary conditions, the problem in eq 1 is solved, and the polarization of the medium is represented by an ASC density $\sigma(\mathbf{s})$ with $\mathbf{s} \in \Gamma$. The ASC density is the solution of an integral equation whose form varies according to which member of the PCM family of models is being used. The integral equation formalism PCM (IEFPCM)^{23–25} (hereafter simply called “PCM”) is the model of choice because of its broader applicability to all values of ε and because it represents the optimal compromise between accuracy and formal complexity. The integral equation for the PCM model reads

$$\left(\frac{\varepsilon+1}{\varepsilon-1} \hat{\mathcal{J}} - \frac{1}{2\pi} \hat{\mathcal{D}} \right) \hat{\mathcal{J}} \sigma(\mathbf{s}) = - \left(\hat{\mathcal{J}} - \frac{1}{2\pi} \hat{\mathcal{D}} \right) \Phi(\mathbf{s}) \quad (3)$$

where $\Phi(\mathbf{r})$ is the solute's electrostatic potential, $\hat{\mathcal{J}}$ is the identity operator, while $\hat{\mathcal{J}}$ and $\hat{\mathcal{D}}$ (together with its adjoint $\hat{\mathcal{D}}^*$) are components of the so-called Calderon projector.²⁶ Their expressions are defined as

$$\hat{\mathcal{J}}\sigma(\mathbf{s}) = \int_{\Gamma} \frac{\sigma(\mathbf{s}')}{|\mathbf{s} - \mathbf{s}'|} d^2\mathbf{s}' \quad (4)$$

$$\hat{\mathcal{D}}^*\sigma(\mathbf{s}) = \int_{\Gamma} \left\{ \frac{\partial}{\partial \hat{n}_s} \frac{1}{|\mathbf{s} - \mathbf{s}'|} \right\} \sigma(\mathbf{s}') d^2\mathbf{s}' \quad (5)$$

$$\hat{\mathcal{D}}\sigma(\mathbf{s}) = \int_{\Gamma} \left\{ \frac{\partial}{\partial \hat{n}_{s'}} \frac{1}{|\mathbf{s} - \mathbf{s}'|} \right\} \sigma(\mathbf{s}') d^2\mathbf{s}' \quad (6)$$

where \hat{n}_s is the outward normal direction to the surface at point $\mathbf{s} \in \Gamma$. Taking the limit for a large dielectric constant, the conductor-like PCM^{27–29} (CPCM) model is recovered, which is still very accurate in the case of fairly polar solvents, and it has the advantage of being simpler than the more general dielectric model as the CPCM integral equation reads

$$\hat{\mathcal{J}}\sigma(\mathbf{s}) = -f(\epsilon)\Phi(\mathbf{s}) \quad (7)$$

where $f(\epsilon) = (\epsilon - 1)/\epsilon$.

Practical applications of all PCM models require a discrete representation of the ASC density over the solute–solvent interface. Recently, a CSC formalism,¹² which allows for a robust and smooth definition of all the discretized quantities, has been described. The ASC is expanded in a basis of spherical Gaussian functions:

$$\sigma(\mathbf{r}) = \sum_i \frac{q_i}{a_i} \phi_i(\mathbf{r}; \mathbf{s}_i, \zeta_i) \quad (8)$$

where a_i is the area of the i -th surface element, q_i is the corresponding expansion coefficient of σ (which has the physical dimensions of a charge), and \mathbf{s}_i is the representative point of the i -th surface element. By defining

$$\mathbf{R}_\epsilon = \frac{\epsilon + 1}{\epsilon - 1} \mathbf{1} - \frac{1}{2\pi} \mathbf{D}\mathbf{A} \quad (9)$$

$$\mathbf{T}_\epsilon = \mathbf{R}_\epsilon \mathbf{S} \quad (10)$$

and

$$\mathbf{R}_\infty = \lim_{\epsilon \rightarrow \infty} \mathbf{R}_\epsilon = \mathbf{1} - \frac{1}{2\pi} \mathbf{D}\mathbf{A} \quad (11)$$

the discretized IEFPCM equation reads

$$\mathbf{T}_\epsilon \mathbf{q} = -\mathbf{R}_\infty \mathbf{V} \quad (12)$$

where $\mathbf{V}_i = \Phi(\mathbf{s}_i)$.

As discussed in detail in the first VPCM paper,¹³ the PCM problem can be recast in a variational fashion (VPCM) by defining a suitable functional, whose minimization corresponds to the solution of eq 12. This functional assumes the following form:

$$\mathcal{G}(\tilde{\mathbf{q}}) = \frac{1}{2} \tilde{\mathbf{q}}^\dagger \tilde{\mathbf{Y}} \tilde{\mathbf{q}} + \tilde{\mathbf{q}}^\dagger \tilde{\mathbf{V}} = \frac{1}{2} \tilde{\mathbf{q}}^\dagger \mathbf{Y} \tilde{\mathbf{q}} + \tilde{\mathbf{q}}^\dagger \tilde{\mathbf{V}} \quad (13)$$

where $\tilde{\mathbf{q}} = \mathbf{R}_\epsilon^+ \mathbf{q}$, $\tilde{\mathbf{V}} = \mathbf{R}_\infty \mathbf{V}$, and

$$\left(\frac{\mathbf{T}_\epsilon \mathbf{R}_\infty^+ + \mathbf{R}_\infty \mathbf{T}_\epsilon^+}{2} \right) = \frac{\mathbf{Y} + \mathbf{Y}^\dagger}{2} = \tilde{\mathbf{Y}} \quad (14)$$

The minimum of the functional in eq 13 with respect to the $\tilde{\mathbf{q}}$ charges is obtained by setting to zero its first derivative:

$$\frac{\partial \mathcal{G}(\tilde{\mathbf{q}})}{\partial \tilde{\mathbf{q}}} = \tilde{\mathbf{Y}} \tilde{\mathbf{q}} + \tilde{\mathbf{V}} = 0 \quad (15)$$

which is a condition equivalent to the solution of eq 12, as it can be seen by substituting in eq 15 the definitions of the appropriate quantities.

The only molecular property of the solute that appears in the expression of the free energy functional eq 13 is the transformed electrostatic potential $\tilde{\mathbf{V}}$ produced by the solute at the surface Γ . This is defined as

$$\begin{aligned} \mathbf{V}_i &= \sum_{\mu\nu} \left[\frac{\int d^3\mathbf{r} d^3\mathbf{r}' \phi_i(\mathbf{r}; \mathbf{s}_i, \zeta_i) \chi_\mu(\mathbf{r}') \chi_\nu(\mathbf{r}')}{|\mathbf{r} - \mathbf{r}'|} \right] \mathbf{P}_{\mu\nu} \\ &= \sum_{\mu\nu} \mathbf{V}_{\mu\nu} \mathbf{P}_{\mu\nu} \end{aligned} \quad (16)$$

where $\mathbf{P} = \mathbf{C}\mathbf{C}^\dagger$ is the electronic density matrix and \mathbf{C} is the matrix of the molecular orbitals coefficients in the atomic basis set. More precisely eq 16 represents only the electronic term in the electrostatic potential, while the nuclear contribution is constant during the SCF procedure. By means of eq 13, it is possible to define a functional of both the density matrix \mathbf{P} and the transformed polarization charges $\tilde{\mathbf{q}}$ as

$$\mathcal{G}(\mathbf{P}, \tilde{\mathbf{q}}) = \langle \mathbf{h}\mathbf{P} \rangle + \frac{1}{2} \langle \mathbf{G}(\mathbf{P})\mathbf{P} \rangle + \frac{1}{2} \tilde{\mathbf{q}}^\dagger \mathbf{Y} \tilde{\mathbf{q}} + \tilde{\mathbf{q}}^\dagger \langle \tilde{\mathbf{V}}\mathbf{P} \rangle \quad (17)$$

where $\langle \dots \rangle$ denotes the matrix trace, while \mathbf{h} and $\mathbf{G}(\mathbf{P})$ are the usual one- and two-electron matrices. The last term on the right-hand side of eq 17 expresses the explicit dependence of the electrostatic potential on the electronic density \mathbf{P} . By minimizing eq 17 with respect to both \mathbf{P} , which is to be constrained to be idempotent, the following coupled equations are obtained

$$\begin{cases} \mathbf{F}(\mathbf{P}, \tilde{\mathbf{q}})\mathbf{C} = \mathbf{S}\mathbf{C}\epsilon \\ \tilde{\mathbf{Y}} \tilde{\mathbf{q}} = -\tilde{\mathbf{V}}(\mathbf{P}) \end{cases} \quad (18)$$

where

$$\mathbf{F}_{\mu\nu} = \mathbf{h}_{\mu\nu} + \mathbf{G}_{\mu\nu}(\mathbf{P}) + \tilde{\mathbf{V}}_{\mu\nu}^\dagger \tilde{\mathbf{q}}$$

is the Fock operator, including the solute–solvent interaction term. The first line in eq 18 is the well-known Roothan equation, which is nonlinear in the density matrix \mathbf{P} and is coupled to the second set of equations by the dependence of the Fock operator on the PCM charges $\tilde{\mathbf{q}}$. On the other hand, the PCM equations are coupled to the Roothan equations through the dependence of the transformed electrostatic potential on the density matrix.

2.2. Implementation. The convergence of the SCF procedure can be greatly improved by means of Pulay's DIIS^{20,21} extrapolation technique. Indeed, an extrapolation technique is usually required to ensure the convergence of the solution of the Roothan equations, since a straightforward repeated diagonalization is typically very slowly converging or not converging at all.

The idea underlying the DIIS approach is rather simple. Provided a sequence $\{x_j\}$ of points obtained by means of an iterative procedure to minimize a function, an estimate x^{ext} of the solution is obtained by an affine combination of the points with coefficients chosen to minimize a suitable error, for example, the gradient of the function itself. This leads to a linear system of

$N + 1$ equations, where N is the number of points, which can be solved by matrix inversion as N is usually a small number.

When DIIS is applied to help the convergence of the iterative SCF problem, the error vector is built from the commutator of the Fock matrix and the density matrix:

$$\mathbf{e}_i = [\mathbf{F}^i, \mathbf{P}^i]$$

which vanishes when the SCF equation is satisfied. However, it has been proven²² that using only the commutator as a measure of the DIIS error does not guarantee convergence and, in particular, does not guarantee convergence on the electronic ground state, since excited-state solutions are also characterized by vanishing commutators. Including the energy²² as an additional source of error (EDIIS) has been proven to be successful in guiding the SCF toward the ground-state solution.

We point out that if the Fock matrix is linear with respect to the density, as in the case of Hartree–Fock and most semiempirical methods

$$\mathbf{G}(\mathbf{P}^{\text{ext}}) = \tilde{\mathbf{G}}^{\text{ext}}$$

which allows for the extrapolation of the Fock matrix instead of the density, while extrapolating the density will require an additional Fock matrix formation at each SCF cycle. The above relation does not hold exactly in the case of DFT, where the exchange–correlation term in the Fock matrix is not linear in the density; however, it is possible to proceed in the same way. Typically, this will make the convergence of the SCF procedure somewhat slower but not enough to make the procedure involving the proper extrapolation of the density computationally competitive, as the latter requires two Fock matrix formation per cycle.

In our simultaneous optimization approach, we solve the coupled problem, eq 18, with the following procedure. Starting from a guess of both the density matrix \mathbf{P} and the charges $\tilde{\mathbf{q}}$, an update step is performed on both set of variables. The density update step is the standard Fock matrix diagonalization, which provides a new set of molecular orbital coefficients \mathbf{C} , while for the charges a scaled steepest-descent step is computed. We have chosen such a simple update step for the polarization charges because of its better performance when used in connection of the DIIS extrapolation (vide infra). Update methods that require the knowledge of two or more points, such as conjugate gradient or quasi-Newton methods associated with line search, have instead shown a much worse behavior when coupled with the DIIS extrapolation.

In order to compute the update step on the charges $\tilde{\mathbf{q}}$, the product between the relevant PCM matrix and a vector of charges must be evaluated. In the case of the general dielectric model, the $\tilde{\mathbf{Y}}$ matrix is used, while the \mathbf{S} matrix is required for CPCM. Depending on the available memory, the matrix–vector product may be computed on the fly, possibly exploiting a linear scaling technique, such as the fast multipole methods,^{9,30} or the matrix can be fit in memory, and the matrix–vector product carried out with quadratic cost. While the on-the-fly evaluation of the matrix–vector product by the CPCM matrix is very efficient, the $\tilde{\mathbf{Y}}$ matrix is less easily tractable as its formation involves two matrix–matrix multiplications, while the direct evaluation of the matrix–vector products requires four multiplications by \mathbf{S} and two multiplications by \mathbf{D} . Typically, if the available memory allows for the efficient formation of $\tilde{\mathbf{Y}}$, then the matrix is computed, stored in memory or on disk, and reused whenever possible. The availability of the $\tilde{\mathbf{Y}}$ matrix has the additional advantage of providing the exact diagonal elements. These are

used to scale the gradient of functional eq 17 with respect to the charges and therefore compute exactly its minimum along the steepest-descent direction, which has a closed expression in the case of a quadratic form.

From the update step on the density \mathbf{P} we get a new density and therefore a new electrostatic potential:

$$\mathbf{P}^i, \tilde{\mathbf{V}}^i \rightarrow \mathbf{P}^{i+1}, \tilde{\mathbf{V}}^{i+1}$$

while from the update step on the charges we obtain a new set of charges

$$\tilde{\mathbf{q}}^i \rightarrow \tilde{\mathbf{q}}^{i+1}$$

The DIIS extrapolation is then performed for both sets of variables at the same time. As error vector, we choose the sum of the usual DIIS error (i.e., the Fock matrix–density matrix commutator) and the gradient of functional eq 17 with respect to the charges $\tilde{\mathbf{q}}$. The two components of the error vectors are weighed by a suitable constant factor, so that

$$\mathbf{B}_{i,j} = w_F \langle \mathbf{e}_F^i, \mathbf{e}_F^j \rangle + w_Q \langle \mathbf{e}_Q^i, \mathbf{e}_Q^j \rangle \quad (19)$$

where

$$\mathbf{e}_F^i = [\mathbf{F}^i, \mathbf{P}^i], \quad \mathbf{e}_Q^i = \tilde{\mathbf{Y}} \tilde{\mathbf{q}}^i + \tilde{\mathbf{V}}^i$$

In eq 19, \mathbf{B} is the $(N + 1)$ square Pulay's matrix for $i, j \leq N$, and $\langle \cdot, \cdot \rangle$ denotes the canonical scalar product. For EDIIS we simply use the corresponding values of the free energy functional as in eq 17.

In our implementation the two-electron component of the Fock matrix and the PCM gradient are extrapolated. In fact, we note that the functional in eq 17 is the sum of a linear term involving the one-electron matrix \mathbf{h} , whose derivative with respect the density matrix is a constant and of three quadratic terms in the density and the charges. In other words, the quadratic terms in the free energy functional are bilinear with respect to the variables \mathbf{P} and $\tilde{\mathbf{q}}$, and therefore we can extrapolate the two gradients, i.e., the two-electron part of the Fock matrix and the PCM gradient, thanks to their linearity. More in detail, the extrapolation step gives

$$\mathbf{F}_{\mu\nu}^{i+1, \text{ext}} = \mathbf{h}_{\mu\nu} + \mathbf{G}_{\mu\nu}(\mathbf{P})^{i+1, \text{ext}} + \tilde{\mathbf{V}}_{\mu\nu}^+ \tilde{\mathbf{q}}^{i+1, \text{ext}}$$

$$\mathbf{g}^{i+1, \text{ext}} = \tilde{\mathbf{Y}} \tilde{\mathbf{q}}^{i+1, \text{ext}} + \tilde{\mathbf{V}}^{i+1, \text{ext}}$$

where

$$\tilde{\mathbf{V}}^{i+1, \text{ext}} = \langle \tilde{\mathbf{V}} \mathbf{P}^{i+1, \text{ext}} \rangle$$

and we obtain a consistent and coherent extrapolation of both the PCM contribution to the Fock matrix, which depends on the extrapolated charges $\tilde{\mathbf{q}}^{i+1, \text{ext}}$ and the gradient of the free energy functional with respect to the charges, which depends on the extrapolated density $\mathbf{P}^{i+1, \text{ext}}$ through the extrapolated transformed potential.

3. NUMERICAL TESTS

In this section, we report some numerical results obtained with the procedure previously described in section 2. First, we discuss the significance of the few parameters that control the behavior of the algorithm and the choice of their optimal value. Then we describe the results obtained on several medium- to large-sized systems, and we compare them with the corresponding ones obtained with the traditional approaches.

All the calculations have been performed with the development version of the Gaussian suite of programs.³¹

3.1. Setup Calculations. There are three main issues involved in the set up of a simultaneous solution algorithm which will optimize the density matrix and the polarization charges, as described in Section 2. First, an initial guess for the values of the polarization charges must be formulated. Then, the optimal relative weights for the two components w_F and w_Q of the DIIS error in eq 19 must be established, and last, a suitable convergence criterion must be set on the PCM polarization charges or on the gradient of the free energy functional with respect to the charges.

We explored various possible choices for the initial guess of the polarization charges. In particular, we considered: (i) simply starting from zero charges; (ii) using a uniform distribution of charges summing up to the solute total charge; (iii) obtaining the initial charges from a diagonal approximation of the PCM equations, i.e., as

$$\tilde{q}_i^0 = -\frac{\tilde{V}_i^0}{\tilde{Y}_{ii}}$$

or (iv) from a low-accuracy solution of the PCM equations using an iterative procedure with a convergence criteria on the root-mean-square (rms) charge residue in the range of 10^{-1} – 10^{-4} . In many instances we found that starting from partially converged charges improves only slightly the overall convergence of the SCF procedure, while adding an extra computational cost that could be significant depending on the size of the system and the choice of the one-electron Hamiltonian. Our conclusion is therefore to set all the charges to zero as initial guess.

The optimal choice of the relative weights for the two components of the DIIS error, as in eq 19, has been achieved by considering the following. It should be realized immediately that the absolute value of the two components of the error may differ by orders of magnitude. In particular, at the beginning of the SCF procedure, the guess for the density is generally good as it corresponds to the diagonalization of a Fock matrix based on the Harris functional.³² Moreover, our choice of the initial guess for the polarization variables is likely to make the initial error on the charges consistently much larger than the one on the density. The big difference in the initial values of the two error components may lead to DIIS coefficients that overestimate the effect of the changes in the PCM terms of the energy functional. This, in turn, is likely to affect in a negative way the overall convergence behavior. Indeed, it has become apparent from our tests that the effect of the changes in the density is the most important one. Especially when the iterative procedure is still far from the solution, it is crucial to make the change in the density and not the change in the PCM charges, the driving force in the DIIS extrapolation. For this reason, we decided to weight the density error with a larger coefficient. After analyzing the results of a number of tests, we concluded that a good value for the ratio between w_F and w_Q is 1000:1. This ratio leads to contributions to the Pulay's DIIS matrix from the two sources of error, of roughly the same order of magnitude, while at the beginning of the SCF procedure, the density component of the error is somewhat larger. We point out that this is an arbitrary empirical choice, which is the result of a limited set of numerical tests, and it is likely to be just an approximation of the optimal weighing of the two error components. We set $w_F = 1$ and $w_Q = 0.001$, as this choice has led to good convergence behavior using both semiempirical and HF or DFT Hamiltonians.

Table 1. Systems Studied^a

	alias	N_{at}	N_{ch}	charge
diphthamide	—	48	3185	+1
cevine	—	73	3816	0
dammarane	—	84	4055	0
tuftsin	—	77	4866	0
Ca(heme)	—	73	4990	−2
substituted guanidine	sGua	84	5327	+2
Ac(Ala) ₉ NH	Ala9	99	6030	0
taxol	—	113	6460	0
(Ala) ₂₅	Ala25	259	13 767	0
(dA–dT) ₅	DNA-5	318	17 202	−8
(dA–dT) ₆	DNA-6	382	19 979	−10
(dA–dT) ₇	DNA-7	510	26 473	−12
crambin	—	642	30 271	0

^a N_{at} = number of atoms, N_{ch} = number of PCM charges, Ac = acetyl, Ala = alanine, dA = deoxyadenosyne, and dT = deoxythymine.

Finally, the convergence criterion for the polarization charges must be chosen so that the simultaneous variational minimization of the free energy functional in eq 17 is accurate enough to be used in a solute geometry optimization. In other words, the rms norm of the derivatives of eq 17 with respect to the polarization charges must be small enough that they will not reduce the accuracy of the forces, i.e., the derivatives of the free energy with respect to the atomic positions. Thus, we compared the final values of both energy and forces obtained requiring the rms norm of the PCM charge gradient to be smaller than 10^{-N} (and its maximum element to be smaller than 10^{-N+1}), with the values obtained by solving “exactly” the PCM equations by means of matrix inversion with iterative refinement (within double precision). Considering the results of a number of tests, we choose N so that the differences in energy were consistently smaller than 10^{-7} Hartrees and the rms and maximum difference in the forces were smaller than the thresholds currently used in a “very tight” geometry optimization (rms force $< 10^{-5}$ and maximum force $< 2 \times 10^{-5}$). Our results obtained using the PM6³ semiempirical method for a set of small- to medium-sized solutes show that $N = 4$ is usually enough for the requirements set forth above to be met.

3.2. Numerical Results. In this section, we report the results obtained for a set of molecules using both the CPCM and IEFCPCM in their standard and variational formulation. The molecular structures are available in the Supporting Information.

To better understand the “computational size” of the systems we studied, we list in Table 1 the number of atoms (N_{at}) and the number of surface elements, i.e. the number of PCM charges N_{ch} for each solute, and we also include the value of the total charge.

We have included in our test set medium- to large or very large-sized molecules. Some of the test solutes are charged either positively or negatively in order to better explore the convergence of our algorithm in cases where the total surface charge does not add up to zero. Moreover, we performed calculations in water ($\epsilon = 78.3553$) (Tables 2 and 5), dichloromethane ($\epsilon = 8.93$) (Table 3), and cyclohexane ($\epsilon = 2.0165$) (Table 4) to test the behavior of the method with strongly polar, polar, and nonpolar solvents. All the calculations have been performed using the PM6 semiempirical method to describe the solute.

For the first set of molecules, we report in each table the number of SCF iterations and the relative total elapsed time with respect to the standard algorithm which employs matrix

Table 2. Results Obtained in Water^a

	variational		iterative		inversion
	N_{it}	time	N_{it}	time	N_{it}
PCM					
diphthamide	39	72.73	16	457.58	16
cevane	31	91.18	15	580.88	15
dammarane	40	140.32	15	812.90	15
tuftsin	50	111.51	15	595.68	15
Ca(heme)	44	65.04	22	311.19	22
sGua	40	95.54	15	286.61	15
Ala9	41	88.35	14	530.52	14
taxol	47	95.77	19	750.81	19
Ala25	49	65.76	14	139.23	14
CPCM					
diphthamide	32	75.00	16	100.00	16
cevane	28	106.67	15	213.33	15
dammarane	27	102.86	15	242.86	15
tuftsin	31	98.28	15	244.83	15
Ca(heme)	36	51.61	22	120.97	22
sGua	33	70.15	15	65.67	15
Ala9	32	85.05	14	226.17	14
taxol	38	93.38	19	321.32	19
Ala25	34	49.38	14	58.31	14

^a Timings are reported as a percentage of the time required for the matrix inversion procedure.

Table 3. Results Obtained in Dichloromethane^a

	variational		iterative		inversion
	N_{it}	time	N_{it}	time	N_{it}
PCM					
diphthamide	34	100.00	16	281.25	16
cevane	30	117.31	15	740.38	15
dammarane	33	119.05	15	806.35	15
tuftsin	43	98.56	15	558.99	15
Ca(Heme)	43	62.94	22	302.10	22
sGua	35	85.83	15	220.00	15
Ala9	34	77.29	14	534.66	14
taxol	43	88.60	19	749.51	19
Ala25	37	55.21	14	126.27	14
CPCM					
diphthamide	33	86.36	16	90.91	16
cevane	28	106.67	15	220.00	15
dammarane	28	105.71	15	248.57	15
tuftsin	29	88.14	15	238.98	15
Ca(Heme)	36	53.33	21	118.33	21
sGua	32	64.29	15	62.86	15
Ala9	32	85.05	14	230.84	14
taxol	41	101.48	19	322.96	19
Ala25	35	52.74	14	43.66	14

^a Timings are reported as a percentage of the time required for the matrix inversion procedure.

Table 4. Results Obtained in Cyclohexane^a

system	variational		iterative		inversion
	N_{it}	time	N_{it}	time	N_{it}
IEFPCM					
diphthamide	34	118.52	15	344.44	15
cevane	28	109.43	15	750.94	15
dammarane	27	104.84	15	795.16	15
tuftsin	37	118.45	15	800.00	15
Ca(Heme)	44	92.93	21	423.23	21
sGua	35	129.13	15	250.49	15
Ala9	32	101.65	14	731.32	14
taxol	40	114.10	19	1089.16	19
Ala25	35	78.56	14	191.19	14
CPCM					
diphthamide	36	84.00	15	64.00	15
cevane	32	123.33	15	216.67	15
dammarane	30	111.43	15	257.14	15
tuftsin	36	111.86	15	235.59	15
Ca(Heme)	45	67.80	21	118.64	21
sGua	40	67.06	15	74.12	15
Ala9	33	87.85	14	230.84	14
taxol	42	103.70	19	320.00	19
Ala25	37	52.66	14	42.77	14

^a Timings are reported as a percentage of the time required for the matrix inversion procedure.

inversion to solve the PCM equations. We list both the variational solution algorithm of Section 2 and the standard algorithm using an iterative approach to solve the PCM equations. We do not report the absolute timings to avoid unfair comparisons of results obtained with different computational resources.

Before discussing the results, we offer a few preliminary considerations. The relative efficiency of the standard inversion, standard iterative, and variational algorithm depends on the interplay of a number of factors, and a complete exploration of this complex landscape is beyond the scope of this contribution. The standard inversion approach is characterized by an $\mathcal{O}(N_{ch}^3)$ computational cost and an $\mathcal{O}(N_{ch}^2)$ memory requirement. In the case of CPCM the only cubic step is the matrix inversion, while the formation of the IEF matrix involves two additional matrix multiplications. On the other hand, in both the standard iterative and the variational algorithm, the matrix can be held in memory so that each iteration would have quadratic cost (matrix–vector product). However, in the case of IEF this would not change the cost of forming the matrix which would still be a $\mathcal{O}(N_{ch}^3)$ step. The alternative would be to hold in memory the **S** and **D** matrices which are required to build the IEF matrix, therefore “trading” the cost of a single cubic step for the cost six matrix–vector products per iteration and also replacing the exact diagonals of the IEF matrix with the diagonals of the **S** matrix, which are less effective as a preconditioner in the iterative solutions. Finally, a definitive assessment of the relative performance of the three algorithm will require the exploration of the linear scaling regime where the contraction of the **S** and **D** matrices with the charge vector is carried out with $\mathcal{O}(N_{ch})$ cost by means of the fast multipole method.

The standard solution by matrix inversion is the fastest method for small systems, where the $\mathcal{O}(N_{ch}^3)$ step does not

Table 5. Results for larger molecules in water.^a

	PCM				CPCM			
	variational		iterative		variational		iterative	
	N_{it}	time	N_{it}	time	N_{it}	time	N_{it}	time
DNA-5	76	53 min	34	3 h 37 min	55	17 min	28	30 min
DNA-6	96	1 h 28 min	34	4 h 46 min	49	21 min	33	45 min
DNA-7	118	3 h 15 min	29	9 h 28 min	61	46 min	36	1 h 46 min
crambin	160	5 h 20 min	57	33 h 15 min	121	1 h 53 min	57	4 h 29 min

^a All the calculations have been performed on a dual Xeon E5530/48GB RAM computer.

emerge as a bottleneck in the overall SCF calculation. On the other hand, as soon as the dimension of the system increases, the variational procedure, whose timings are nevertheless comparable with the inversion even for smaller systems, becomes a competitive alternative. It is not unexpected that an iterative approach replacing the cubic step in the number of surface elements is the only viable option for the study of large systems. For the IEF model, the variational procedure is always faster than the standard iterative solution of the equations. The comparison is more significant for CPCM, where the variational procedure competes with a very efficient standard iterative solver. For molecular sizes where the iterative procedure begins to be competitive with the matrix inversion, the standard approach is sometimes faster than the variational one, especially in the case of nonpolar solvents. Nevertheless, the overall number of matrix–vector products required by the standard iterative approach increases fairly rapidly with the dimensions of the system, and this makes the variational approach the most promising one, even for CPCM when applied to larger solute. We notice that in the case of charged systems, the variational approach shows a very good convergence behavior, resulting in the majority of cases faster than the standard iterative procedure.

In Table 5 we report some results of calculations on increasingly large systems, from 318 up to 642 atoms. We notice that the DNA fragments are heavily charged, as we did not add counterions. Indeed, we want to make sure that the variational algorithm does not show stability issues when solving for polarization charges that do not sum up to zero but rather correspond to a huge solute–solvent interaction energy. All the calculations reported in Table 5 have been performed on a dual Xeon E5530 workstation (hyper-threading was disabled) equipped with 48 GB of RAM. In this case, we report the absolute elapsed time.

As expected, the variational approach outperforms the standard iterative one for both PCM and CPCM. In particular, the comparison with CPCM proves our assumption that the variational procedure is probably the best choice for large systems, under the assumption that the one-electron model Hamiltonian being used does not represent the computational bottleneck. We also point out that, because of the challenges involved in standard iterative solution for IEF, the variational approach introduced in this work is already a viable alternative to the matrix inversion, even for fairly small systems.

4. CONCLUSIONS

In this paper we have introduced a new strategy (VPCM) to solve the Roothan equations coupled with the PCM equations. We define a free energy functional of both the electronic density and the polarization charges whose variational minimization, using alternate steps in the two variable spaces, leads to the free

energy in solution including the mutual polarization of the solute and the dielectric continuum. This approach is computationally advantageous when dealing with large systems, where the solution of the PCM problem may become the dominant step in terms of computational cost, because an approximate one-electron Hamiltonian is used.

We think that this methodology could be efficiently applied to multiscale methods where a core system is described using an accurate level of theory, while the rest of the solute is treated with a computationally cheaper approach. In this context, the introduction of solvent effects by means of PCM can easily become the computational bottleneck because of the large size of the solute. Therefore, we expect the new approach introduced in this paper to be particularly relevant in the case of ONIOM^{33–35} calculations. Indeed, the availability of an efficient method to study large to very large systems coupled to a dielectric continuum would be an important tool for the description of biological systems in solution.

■ ASSOCIATED CONTENT

S Supporting Information. Geometries of the studied molecules. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: flipparini@sns.it.

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