

Analytical First and Second Derivatives for a Fully Polarizable QM/Classical Hamiltonian

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S Supporting Information

ABSTRACT: In this work, we present the derivation and implementation of analytical first and second derivatives for a fully polarizable QM/MM/PCM energy functional. First derivatives with respect to both QM- and MM-described nuclear coordinates and electric perturbations are derived and implemented, and some preliminary application is shown. Analytical second derivatives with respect to nuclear and electric perturbations are then derived, and some numerical test is presented both for a solvated system and for a chromophore embedded in a biological matrix.

1. INTRODUCTION

In recent years, the combined quantum mechanics/molecular mechanics^{1–9} (QM/MM) approach has played an increasing role in the explicit modeling of environmental effects. While MM methods on their own are generally only able to describe environmental effects on classical properties, QM/MM methods allow one to examine environmental effects on properties that require a QM description. In the specific case of spectroscopic measurements, the probe, sometimes together with a few neighboring groups, is treated at the QM level of theory, whereas the more distant environment is described by a MM force field. As a matter of fact, the molecular environment interacting with the probe, although often neglected in a first approximation, can be extremely important in predicting spectroscopic outcomes. The probe geometry can be modified by the environment (mechanical embedding), but, more importantly, the electronic structure of the probe can be altered by the environment through electrostatic and/or polarization effects (electrostatic embedding). For processes occurring in solution, proper boundary conditions^{10–14} must next be employed for describing bulk effects. Here, continuum solvent models^{15,16} come into play, since they allow an effective treatment of the most important intermolecular interactions (electrostatic, dispersion, repulsion) in a very effective way. In the following, we will refer, in particular, to the so-called polarizable continuum model (PCM),^{17–25} which is one of the most physically sound and numerically efficient approaches devised so far. It is noteworthy that, while PCM includes polarization effects, in most cases the MM part is able to describe only electrostatic effects, with one noticeable exception.²² This incongruence prompted us to introduce an integrated QM/MM/PCM approach in which also the MM part includes polarization effects by the so-called fluctuating charge (FQ)^{26–43} approach.

As a first step, energy and analytical forces have to be defined in order to allow for geometry optimizations and/or molecular dynamics (MD) simulations. However, the simulation of spectra requires also the description of excited electronic states

(for UV–vis and related spectroscopies) and the availability of analytical Hessians for an effective computation of vibrational spectra at the harmonic and, even more, anharmonic levels. Furthermore, analytical derivatives with respect to electric fields are needed to compute intensities and other transition properties. The FQ model has already been used in combination with semiempirical and *ab initio* QM Hamiltonians for energy and first derivatives.^{44–46} To the best of our knowledge, this is the first formulation and implementation of analytical second derivatives for a QM/FQ Hamiltonian and of both first and second derivatives for a QM/FQ/PCM one. An implementation of analytical first derivatives for a similar polarizable QM/MM model, namely the effective fragment potential method,⁴⁷ has been proposed also when the PCM embedding is included in the description.^{48,49} On these grounds, the main aim of the present paper is to report our effective implementation of energies, together with analytical gradients and Hessians for the complete QM/FQ/PCM model whenever the QM part is described by Hartree–Fock or Kohn–Sham (including hybrid functionals) approaches. Some case studies (pyridine in aqueous solution and retinal in a rhodopsin mimic) are then reported to illustrate the status and perspectives of our approach.

Such a model has also been extended by some of us to evaluate ground and excited state energies at the Self Consistent Field (SCF) and Time-Dependent SCF (TD-SCF) levels of theory.⁵⁰

The paper is organized as follows: Section 2 briefly recaps the basic foundations of our model for the evaluation of the ground state energies; analytical expressions for energy first derivatives are also reported. In Section 3, free energy analytical second derivatives are derived, and a modified CPHF procedure is presented. Section 4 reports some preliminary numerical results. Finally, in Section 5, concluding remarks end the presentation.

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2. THEORY

Notation. We will use the bold font to indicate vectors and matrices as a whole, while we will use the normal font for their elements. For instance, \mathbf{P} refers to the density matrix, whose elements are $P_{\mu\nu}$. \mathbf{q} is the vector composed of all of the FQs, while the i th charge is q_i , and \mathbf{F} is the representation matrix of the Fock operator in some basis set. If a quantity is both a matrix (i.e., with respect to the atomic basis set) and a vector (i.e., with respect to the charges manifold), we will use the bold font when we deal with the whole vector irrespectively of the matrix attribute. As an example, we will denote with $\mathbf{V}_{\mu\nu}$ the vector made of the matrices $V_{\mu\nu,i}$ so that, for instance

$$\mathbf{q}^\dagger \mathbf{V}_{\mu\nu} = \sum_i q_i V_{\mu\nu,i}$$

We will use the accent \sim to denote quantities including a FQ contribution: for instance, $\tilde{\mathbf{F}}$ will be the FQ corrected Fock matrix. Finally, we will use superscripts to denote analytical derivatives and put them between parentheses when we mean only the explicit contributions (i.e., the partial derivative).

In the fluctuating charge model, each atom is endowed with a charge, whose value depends on the environment^{26,51,52} according to the electronegativity equalization principle.^{28,53} A convenient formulation of this theory is to define FQs as such minimizing the following functional:

$$\begin{aligned} F(\mathbf{q}, \lambda) &= \sum_{\alpha,i} q_{\alpha} \chi_{\alpha i} + \frac{1}{2} \sum_{\alpha,i} \sum_{\beta,j} q_{\alpha} J_{\alpha i, \beta j} q_{\beta j} \\ &\quad + \sum_{\alpha} \lambda_{\alpha} \left(\sum_i q_{\alpha i} - Q_{\alpha} \right) \\ &= \mathbf{q}^\dagger \boldsymbol{\chi} + \frac{1}{2} \mathbf{q}^\dagger \mathbf{J} \mathbf{q} + \boldsymbol{\lambda}^\dagger \mathbf{q} \end{aligned} \quad (1)$$

where the Greek indexes α and β run on molecules and the Latin ones, on the atoms of each molecule. In eq 1, a set of Lagrangian multipliers λ_{α} is used to impose charge conservation constraints; by introducing a compact notation (see ref 27), the stationarity conditions read

$$\mathbf{D} \mathbf{q}_{\lambda} = -\mathbf{C}_{\mathbf{Q}} \quad (2)$$

where $\mathbf{C}_{\mathbf{Q}}$ is a vector containing atomic electronegativities and total charge constraints, whereas \mathbf{q}_{λ} is a vector containing charges and Lagrange multipliers.

The coupling with a QM (SCF) description is introduced by treating the interaction between the two densities of charge (i.e., the one produced by the FQs and the QM one) classically, i.e., through a simple Coulomb interaction:

$$E_{\text{QM/MM}} = \sum_{i=1}^{N_q} \Phi[\rho_{\text{QM}}](\mathbf{r}_i) q_i \quad (3)$$

where $\Phi[\rho_{\text{QM}}](\mathbf{r}_i)$ is the electrostatic potential due to the QM density of charge at the i th FQ placed at \mathbf{r}_i

$$\begin{aligned} \Phi[\rho_{\text{QM}}](\mathbf{r}_i) &\stackrel{\text{def}}{=} V_i^e(\mathbf{P}) \\ &= V_i^N(\mathbf{P}) + V_i^e(\mathbf{P}) \\ &= \sum_{\zeta=1}^{N_n} \frac{Z_{\zeta}}{|\mathbf{r}_i - \mathbf{R}_{\zeta}|} - \int_{\mathbf{R}^3} d\mathbf{r} \frac{\rho^{\text{el}}(\mathbf{r})}{|\mathbf{r}_i - \mathbf{r}|} \end{aligned}$$

Here, the ζ -labeled sum runs over the N_n QM nuclei, whose position we call \mathbf{R}_{ζ} (see ref 50 for a detailed discussion of the coupling).

By expanding the electronic density $\rho^{\text{el}}(\mathbf{r})$ in terms of an atomic basis set, the second term of the electrostatic potential becomes

$$V_i^e(\mathbf{P}) = - \sum_{\mu\nu} P_{\mu\nu} \int_{\mathbf{R}^3} d\mathbf{r} \frac{\chi_{\mu}(\mathbf{r}) \chi_{\nu}(\mathbf{r})}{|\mathbf{r}_i - \mathbf{r}|} = \sum_{\mu\nu} P_{\mu\nu} V_{\mu\nu,i} \quad (4)$$

where the “uncontracted” potential $V_{\mu\nu}$ is introduced and the double sum runs on the atomic orbitals. This yields a QM/MM energy functional that is variational with respect to both densities, once the suitable constraints have been taken into account, similar to what has been proposed by one of the present authors for the PCM.^{54,55} Therefore

$$\begin{aligned} \mathcal{E}[\mathbf{P}, \mathbf{q}, \lambda] &= \text{tr } \mathbf{h} \mathbf{P} + \frac{1}{2} \text{tr } \mathbf{P} \mathbf{G}(\mathbf{P}) + \mathbf{q}^\dagger \boldsymbol{\chi} + \frac{1}{2} \mathbf{q}^\dagger \mathbf{J} \mathbf{q} + \boldsymbol{\lambda}^\dagger \mathbf{q} \\ &\quad + \mathbf{q}^\dagger \mathbf{V}(\mathbf{P}) \end{aligned} \quad (5)$$

where \mathbf{h} and \mathbf{G} are the usual one- and two-electron matrices. The coupled equations are hence defined by introducing an effective Fock matrix

$$\tilde{F}_{\mu\nu} = \frac{\partial \mathcal{E}}{\partial P_{\mu\nu}} = h_{\mu\nu} + G_{\mu\nu}(\mathbf{P}) + \mathbf{q}^\dagger \mathbf{V}_{\mu\nu} \quad (6)$$

and the FQs are obtained by imposing the stationarity of the global functional with respect to the charges and the Lagrangian multipliers. When the FQs are coupled to a QM density, a new source term appears in eq 2:

$$\mathbf{D} \mathbf{q}_{\lambda} = -\mathbf{C}_{\mathbf{Q}} - \mathbf{V}(\mathbf{P}) \quad (7)$$

Such a term represents the coupling between the QM and MM portions of the system. The inclusion of a further layer treated by means of the PCM approach (in particular, we will refer to the conductor-like PCM^{56–59}) is easily obtained by redefining the charges and the \mathbf{D} matrix so as to also include PCM contributions, i.e.

$$\begin{pmatrix} \mathbf{D} & \boldsymbol{\Omega}^\dagger \\ \boldsymbol{\Omega} & \mathbf{S}/f(\epsilon) \end{pmatrix} \begin{pmatrix} \mathbf{q}_{\lambda} \\ \boldsymbol{\sigma} \end{pmatrix} = \begin{pmatrix} -\mathbf{C} \\ \mathbf{0} \end{pmatrix} \quad (8)$$

where \mathbf{S} and $\boldsymbol{\Omega}$ represent the Coulomb interaction of the PCM charges with themselves and with the FQs, respectively. In addition, a PCM contribution $\boldsymbol{\sigma}^\dagger \mathbf{V}_{\mu\nu}$ is to be added to $\mathbf{q}^\dagger \mathbf{V}_{\mu\nu}$ in eq 6. Because the inclusion of PCM does not add anything to the theoretical framework but only makes the notation more cumbersome, in the following we will only deal with the QM/FQ contributions, and therefore we will assume tacitly that slight modifications are to be implemented to include the PCM layer. Further details on the coupling of the PCM with the FQ model can be found elsewhere.^{27,50}

2.1. Analytical Energy First Derivatives. The energy first derivative can be expressed by means of the chain rule:⁶⁰

$$\mathcal{E}^x(\mathbf{P}, \mathbf{q}, \lambda) = \frac{\partial \mathcal{E}}{\partial x} + \frac{\partial \mathcal{E}}{\partial \mathbf{P}} \frac{\partial \mathbf{P}}{\partial x} + \frac{\partial \mathcal{E}}{\partial \mathbf{q}} \frac{\partial \mathbf{q}}{\partial x} + \frac{\partial \mathcal{E}}{\partial \boldsymbol{\lambda}} \frac{\partial \boldsymbol{\lambda}}{\partial x}$$

The last two terms vanish because of the stationarity conditions. The first term, which is the partial derivative of the energy with respect to the position of a QM-described nucleus, is

$$\frac{\partial \mathcal{E}}{\partial \mathbf{x}} = \text{tr } \mathbf{h}^x \mathbf{P} + \frac{1}{2} \text{tr } \mathbf{G}^{(x)}(\mathbf{P}) \mathbf{P} + \mathbf{q}^\dagger \mathbf{V}^{(x)}(\mathbf{P}) \quad (9)$$

where

$$V_i^{(x)}(\mathbf{P}) = \sum_{\mu\nu} P_{\mu\nu} V_{\mu\nu,i}^x + \text{nuclear contribution} \quad (10)$$

$$= \frac{Z_\zeta}{|\mathbf{R}_\zeta - \mathbf{r}_i|^2} - \sum_{\mu\nu} \left\langle \frac{\partial(\chi_\mu \chi_\nu)}{\partial \mathbf{R}_\zeta} \left| \frac{1}{|\mathbf{r} - \mathbf{r}'|} \right| \delta(\mathbf{r}' - \mathbf{r}_i) \right\rangle P_{\mu\nu} \quad (11)$$

The term involving the derivatives of the density matrix can be computed starting from the idempotency condition, which gives rise to the usual energy-weighted density matrix contribution

$$-\mathbf{P} \tilde{\mathbf{F}} \mathbf{P}_{\text{oo}}^x = -\tilde{\mathbf{W}} \mathbf{S}_{\text{oo}}^x$$

where the subscript oo denotes the occupied–occupied block of the matrix in the MO basis. Finally

$$\mathcal{E}^x(\mathbf{P}, \mathbf{q}, \lambda) = \text{tr } \mathbf{h}^x \mathbf{P} + \frac{1}{2} \text{tr } \mathbf{G}^{(x)}(\mathbf{P}) \mathbf{P} + \mathbf{q}^\dagger \mathbf{V}^{(x)}(\mathbf{P}) - \text{tr } \mathbf{W} \mathbf{S}_{\text{oo}}^x \quad (12)$$

The derivative of the energy with respect to the position of a MM atom, which we will denote with the superscript ξ , can be obtained using again the chain rule. Only explicit contributions arise, as the overlap matrix does not depend on the position of the MM atoms:

$$\mathcal{E}^\xi(\mathbf{P}, \mathbf{q}, \lambda) = \frac{1}{2} \mathbf{q}^\dagger \mathbf{J}^\xi \mathbf{q} + \mathbf{q}^\dagger \mathbf{V}^{(\xi)}(\mathbf{P}) \quad (13)$$

where the derivative of the QM/MM interaction energy can be seen as the electric field produced by the QM density acting on the FQs:

$$\begin{aligned} V_i^{(\xi)}(\mathbf{P}) &= - \sum_{\zeta} \frac{Z_\zeta (\mathbf{R}_\zeta - \mathbf{r}_i)}{|\mathbf{R}_\zeta - \mathbf{r}_i|^3} + \sum_{\mu\nu} P_{\mu\nu} \langle \chi_\mu \chi_\nu | \\ &\quad \frac{\mathbf{r} - \mathbf{r}'}{|\mathbf{r} - \mathbf{r}'|^3} | \delta(\mathbf{r}' - \mathbf{r}_i) \rangle \\ &= \mathbf{E}_i(\mathbf{P}) \end{aligned}$$

3. ANALYTICAL FORMULATION OF ENERGY SECOND DERIVATIVES

In this section, we will derive working expressions for the analytical second derivatives of the QM/FQ energy functional with respect to nuclear (or electric) perturbations. According to the philosophy of focused models, we will assume that the external perturbation (i.e., the electric field or a nuclear displacement) only acts on the QM portion of the system: we will hence only consider indirect effects on the MM part through the perturbation on the QM density. For the sake of completeness, the full Hessian is derived in Appendix A. Such a choice is consistent with the so-called Partial Hessian Vibrational Approach^{61–67} (PHVA), which we will discuss in the following section. We notice that the direct, analytical approach we present is not feasible when the QM and MM portions are covalently bound: on the other hand, alternative approaches like the ONIOM^{68,69} extrapolation are a possible way to deal with such a situation and a polarizable embedding. If one neglects the nonadditive contributions to the low-level energy in the ONIOM scheme and no covalent bond is present,

the analytical QM/MM derivative scheme is trivially recovered.⁶⁹

The energy second derivative with respect to a perturbation acting on the QM portion of the system can be obtained by differentiating eq 12. By exploiting once again the chain rule and writing explicitly all the contributions:

$$\begin{aligned} \mathcal{E}^{xy} &= \sum_{\mu\nu} \left[h_{\mu\nu}^{xy} + \frac{1}{2} G_{\mu\nu}^{(xy)}(\mathbf{P}) + \mathbf{q}^\dagger \mathbf{V}_{\mu\nu}^{xy} \right] P_{\mu\nu} - \text{tr } \mathbf{W} \mathbf{S}^{xy} \\ &\quad - \text{tr } \mathbf{W}^y \mathbf{S}^x \\ &\quad + \sum_{\mu\nu} [h_{\mu\nu}^x + G_{\mu\nu}^{(x)}(\mathbf{P}) + \mathbf{q}^\dagger \mathbf{V}_{\mu\nu}^x] P_{\mu\nu}^y \\ &\quad + \sum_{\mu\nu} \mathbf{q}^y \mathbf{V}_{\mu\nu}^x P_{\mu\nu} \end{aligned} \quad (14)$$

It is hence necessary to compute the derivatives of the off-diagonal blocks of the density matrix and of the charges, which can be done by means of the so-called Coupled Perturbed Hartree–Fock (CPHF) procedure. Following Frisch and co-workers,⁶⁰ the CPHF equation can be obtained by differentiating once the SCF equations are in their Liouville form:

$$\tilde{\mathbf{F}} \mathbf{P} \mathbf{S} = \mathbf{S} \tilde{\mathbf{F}}$$

$$\tilde{\mathbf{F}}^x \mathbf{P} \mathbf{S} + \tilde{\mathbf{F}} \mathbf{P}^x \mathbf{S} + \tilde{\mathbf{F}} \mathbf{P} \mathbf{S}^x = \mathbf{S}^x \tilde{\mathbf{F}} + \mathbf{S} \tilde{\mathbf{F}}^x + \mathbf{S} \tilde{\mathbf{F}}^x$$

In the MO basis:

$$\tilde{\mathbf{F}}^x \mathbf{P} + \tilde{\mathbf{F}} \mathbf{P}^x + \tilde{\mathbf{F}} \mathbf{P} \mathbf{S}^x = \mathbf{S}^x \tilde{\mathbf{F}} + \mathbf{P}^x \tilde{\mathbf{F}} + \mathbf{P} \tilde{\mathbf{F}}^x$$

By projecting on the ov block, and using the density matrix idempotency and the fact that $[\tilde{\mathbf{F}}, \mathbf{P}] = 0$,

$$\tilde{\mathbf{F}} \mathbf{P}_{\text{ov}}^x + \tilde{\mathbf{F}} \mathbf{S}_{\text{ov}}^x = \mathbf{P}_{\text{ov}}^x \tilde{\mathbf{F}} + \tilde{\mathbf{F}}_{\text{ov}}^x \quad (15)$$

The Fock matrix derivatives can be split into two terms, one which does not involve the derivative of either the density matrix or the charges and the response term:

$$\begin{aligned} \tilde{\mathbf{F}}_{\mu\nu}^x &= h_{\mu\nu}^x + G_{\mu\nu}^{(x)}(\mathbf{P}) + \mathbf{q}^\dagger \mathbf{V}_{\mu\nu}^x + G_{\mu\nu}(\mathbf{P}^x) + \mathbf{V}_{\mu\nu}^\dagger \mathbf{q}^x \\ &= F_{\mu\nu}^{(x)} + \mathbf{q}^\dagger \mathbf{V}_{\mu\nu}^x + G_{\mu\nu}(\mathbf{P}^x) + \mathbf{V}_{\mu\nu}^\dagger \mathbf{q}^x \end{aligned}$$

The FQ derivatives can be obtained by differentiating eq 7:

$$\mathbf{D} \mathbf{q}^x = -\mathbf{V}^{(x)}(\mathbf{P}) - \mathbf{V}(\mathbf{P}^x) \quad (16)$$

Substitution yields

$$\begin{aligned} \tilde{\mathbf{F}}_{\mu\nu}^x &= F_{\mu\nu}^{(x)} + \mathbf{q}^\dagger \mathbf{V}_{\mu\nu}^x - \mathbf{V}_{\mu\nu}^\dagger \mathbf{D}^{-1} \mathbf{V}^x(\mathbf{P}) + G_{\mu\nu}(\mathbf{P}^x) \\ &\quad - \mathbf{V}_{\mu\nu}^\dagger \mathbf{D}^{-1} \mathbf{V}(\mathbf{P}^x) \\ &= \tilde{\mathbf{F}}_{\mu\nu}^{(x)} + G_{\mu\nu}(\mathbf{P}^x) - \mathbf{V}_{\mu\nu}^\dagger \mathbf{D}^{-1} \mathbf{V}(\mathbf{P}^x) \end{aligned} \quad (17)$$

where, coherently with the usual notation, the term

$$\begin{aligned} \tilde{\mathbf{F}}_{\mu\nu}^{(x)} &= h_{\mu\nu}^x + G_{\mu\nu}^{(x)}(\mathbf{P}) + \mathbf{q}^\dagger \mathbf{V}_{\mu\nu}^x - \mathbf{V}_{\mu\nu}^\dagger \mathbf{D}^{-1} \mathbf{V}^{(x)}(\mathbf{P}) \\ &= h_{\mu\nu}^x + G_{\mu\nu}^{(x)}(\mathbf{P}) + \mathbf{q}^\dagger \mathbf{V}_{\mu\nu}^x + \mathbf{V}_{\mu\nu}^\dagger \mathbf{q}^{(x)} \end{aligned}$$

collects all the explicit derivatives of the Fock matrix.

By rearrangement of the terms, the CPHF equations are obtained:

$$\tilde{\mathbf{F}} \mathbf{P}_{\text{ov}}^x - \mathbf{P}_{\text{ov}}^x \tilde{\mathbf{F}} = \tilde{\mathbf{F}}_{\text{ov}}^{(x)} + \mathbf{G}_{\text{ov}}(\mathbf{P}^x) - \mathbf{V}_{\text{ov}}^\dagger \mathbf{D}^{-1} \mathbf{V}(\mathbf{P}^x) - \tilde{\mathbf{F}} \mathbf{S}_{\text{ov}}^x \quad (18)$$

Equation 18 can be rewritten in a formalism that resembles the one commonly used for response theory. In the MO basis

$$G_{pq}(\mathbf{P}^x) = -G_{pq}(\mathbf{S}_{oo}^x) + \sum_{bj} \langle pjl|qb \rangle P_{jb}^x + \langle pbl|qj \rangle P_{bj}^x$$

where

$$\langle pq||rs \rangle = \langle pqlrs \rangle - \langle pqlsr \rangle$$

are standard antisymmetrized bielectronic integrals. Moreover, $\tilde{\mathbf{F}}\mathbf{P}_{ia}^x = \tilde{\epsilon}_i\mathbf{P}_{ia}^x$ and $\mathbf{P}_{ia}^x\tilde{\mathbf{F}} = \tilde{\epsilon}_a\mathbf{P}_{ia}^x$ as the Fock matrix $\tilde{\mathbf{F}}$ is diagonal in the canonical basis set, with $\tilde{\epsilon}_p$ as eigenvalues. If \mathbf{V}_{pq} is the vector formed by the pq matrix elements of the QM/MM interaction potential and

$$\tilde{Q}_{ia} = -\tilde{F}_{ia}^{(x)} + G_{ia}(\mathbf{S}_{oo}^x) + \tilde{\mathbf{F}}\mathbf{S}_{ia} - \mathbf{V}_{ia}^\dagger\mathbf{D}^{-1}\mathbf{V}(\mathbf{S}_{oo}^x)$$

the equations can be recast as

$$\begin{aligned} \epsilon_i^x\mathbf{P}_{ia}^x - \epsilon_a^x\mathbf{P}_{ia}^x = & -\tilde{Q}_{ia} + \sum_{jb} [\langle aj||ib \rangle - \mathbf{V}_{ia}^\dagger\mathbf{D}^{-1}\mathbf{V}_{jb}]P_{jb}^x \\ & + \sum_{jb} [\langle ab||ij \rangle - \mathbf{V}_{ia}^\dagger\mathbf{D}^{-1}\mathbf{V}_{bj}]P_{bj}^x \end{aligned} \quad (19)$$

Taking the adjoint equation and introducing the following matrices (we assume the orbitals to be real)

$$\tilde{A}_{ia,jb} = (\epsilon_a - \epsilon_i)\delta_{ij}\delta_{ab} + \langle aj||ib \rangle - \mathbf{V}_{ia}^\dagger\mathbf{D}^{-1}\mathbf{V}_{jb} \quad (20)$$

$$\tilde{B}_{ia,jb} = \langle ab||ij \rangle - \mathbf{V}_{ia}^\dagger\mathbf{D}^{-1}\mathbf{V}_{bj} \quad (21)$$

one obtains

$$\begin{pmatrix} \tilde{A} & \tilde{B} \\ \tilde{A}^* & \tilde{B}^* \end{pmatrix} \begin{pmatrix} \mathbf{x} \\ \mathbf{y} \end{pmatrix} = \begin{pmatrix} \mathbf{Q} \\ \mathbf{Q}^* \end{pmatrix} \quad (22)$$

where $P_{jb}^x = X_{jb}$ and $P_{bj}^x = Y_{jb}$. The solution to the eqs 22 and 16 gives the derivatives of both the density matrix and the FQs with respect to QM nuclear positions, thus allowing the calculation of energy second derivatives. This result is, of course, coherent to the zero-frequency limit of what was obtained in ref 50.

To summarize, the FQ contributions to analytical second derivatives can be grouped into three categories:

1. explicit contributions:

$$\mathbf{q}^\dagger\mathbf{V}^{(xy)} + \mathbf{q}^{(x)\dagger}\mathbf{V}^{(y)}$$

2. contributions to the explicit Fock matrix derivatives:

$$\mathbf{q}^\dagger\mathbf{V}_{\mu\nu}^x + \mathbf{q}^{(x)\dagger}\mathbf{V}_{\mu\nu}$$

3. contribution to the CPHF matrix:

$$-\mathbf{V}_{ia}^\dagger\mathbf{D}^{-1}\mathbf{V}_{bj}$$

The equations simplify when only electric perturbations are considered: only the CPHF contributions are to be added. However, if an oscillating electric field is considered, the static response picture is not formally justified. Nevertheless, the formalism can be extended to such cases by means of the definition of suitable quasienergy derivatives,⁷⁰ which also applies to PCM solutes^{71,72} and, by extension, to our model.

4. NUMERICAL RESULTS

This section reports some numerical results obtained by applying our newly implemented procedure to a few test cases.

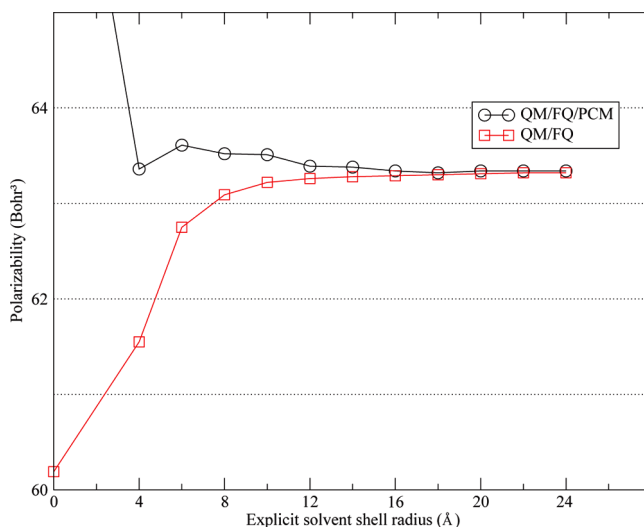


Figure 1. Frequency dependent isotropic polarizability (Bohr^3) of pyrimidine in aqueous solution at 589 nm as a function of the explicit solvent cutting radius, with and without the PCM embedding. The PCM-only result ($R = 0$) is off scale.

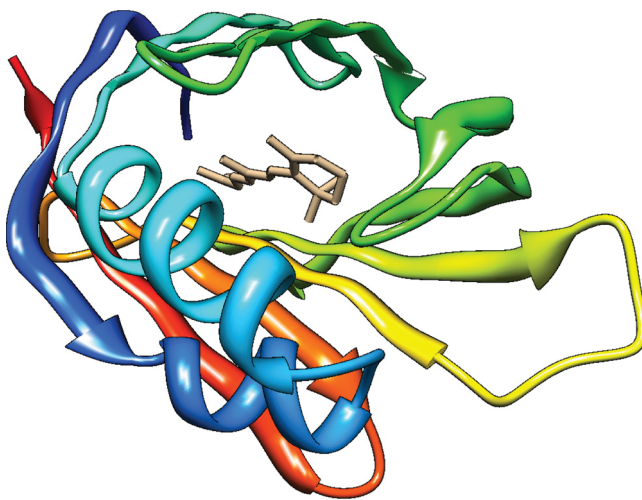


Figure 2. Pictorial view of retinal in a rhodopsin mimic.

First, we will discuss the convergence of the computed properties with respect to the number of explicit solvent molecules and how this is influenced by the presence of the continuum dielectric; an example of geometry optimization will then be discussed, followed by IR spectra calculations.

In order to check the convergence of the computed properties with respect to the number of explicit solvent molecules, we have taken as an example the frequency dependent isotropic polarizability (at 589 nm) of pyrimidine in aqueous solution,^{71,72} including in the picture an increasing number of explicit water molecules (Figure 1). The configurations were taken from a molecular dynamics (MD) simulation,⁷³ and concentric spheres, placed at the center of the pyrimidine molecule were cut and then all of the water molecules whose oxygen atom was inside the sphere included in the atomistic portion. For the QM/FQ/PCM simulations,

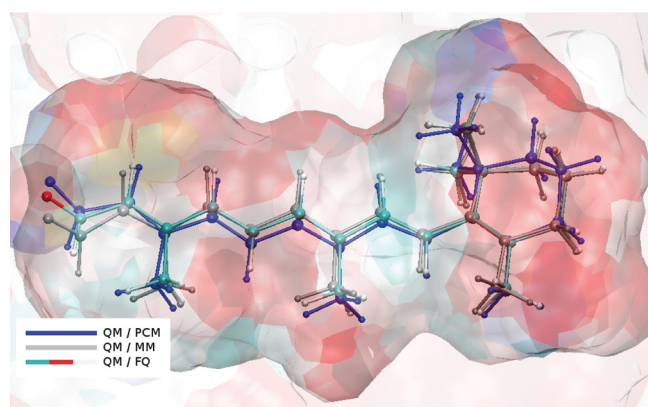


Figure 3. Calculated geometries of retinal in a rhodopsin mimic as obtained at the B3LYP/6-31G* level with different modeling of environmental effects.

Table 1. Selected Distances and Angles for the Retinal Molecule in a Rhodopsin Mimic As Obtained by Exploiting PCM, QM/MM with the AMBER Force Field and the QEq Charges, and QM/FQ

	PCM	QM/MM	QM/FQ
distances (Å)			
l_a : terminal C–O	1.231	1.226	1.235
l_b : chain C–C	1.365	1.365	1.363
l_c : chain C–H	1.086	1.084	1.084
l_d : chain C–CH ₃	1.510	1.514	1.513
l_e : ring C–C	1.513	1.510	1.510
l_f : ring C–CH ₃	1.518	1.518	1.514
l_g : chain length	12.140	12.061	12.228
angle (deg)			
θ_a : chain orientation	90	104	94
dihedral (deg)			
δ_a : chain orientation	−176	−174	−168

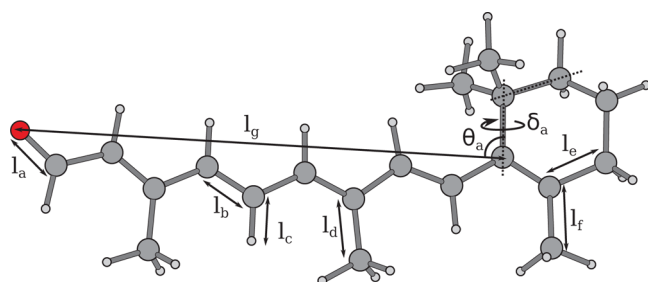


Figure 4. Schematic view of retinal with the indication of selected bond lengths and angles.

the CPCM^{57,58} is used, and a spherical PCM cavity was employed with a radius 1.5 Å larger than that of the cut sphere. The QM solute was described with Density Functional Theory (DFT), using the B3LYP⁷⁴ exchange-correlation functional and the aug-cc-pVTZ⁷⁵ basis set. The parameters for the FQ force field are the ones given by Rick et al.²⁶ $R = 0$ in Figure 1 corresponds to the calculation without the inclusion of explicit solvent molecules, i.e., *in vacuo* or with a standard PCM approach with a molecule shaped cavity, respectively.

The application of the purely continuum PCM approach to the MD snapshot structure causes a large increase in the isotropic polarizability value (see Figure 1). This is not unexpected and shows that long-range interactions, which are

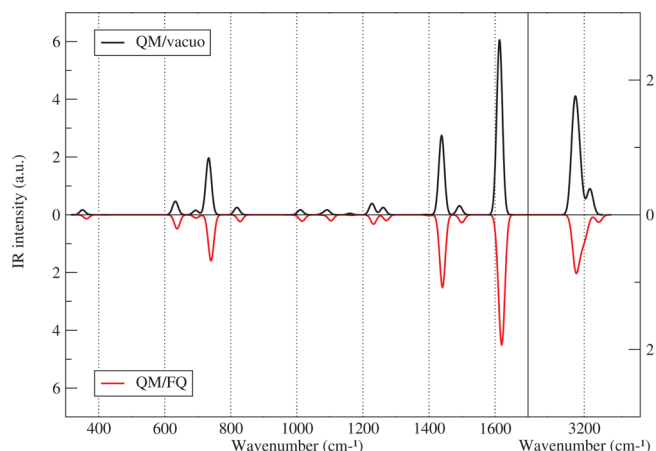


Figure 5. IR spectra of pyrimidine in aqueous solution as calculated for the isolated molecule and with the QM/FQ approach.

taken into account efficiently by the polarizable continuum, play a crucial role in determining the calculated property. Of course, in order to obtain accurate molecular properties of solvated systems, the description of the solvation phenomenon has to be well balanced between long- and short-range effects. In particular, by adding short-range specific solute–solvent interactions, a decrease in the calculated value with respect to the PCM-only description is obtained; i.e., short-range and long-range effects in this case go in the opposite direction. Looking more in detail to convergence, the number of explicit molecules needed to achieve property convergence is huge—a cutting radius of 12–14 Å is necessary; however, as expected, the interplay between specific and long-range interactions is beneficial to reducing the number of explicit solvent molecules to be introduced to reach a given level of accuracy. In fact, in the case of combination with PCM, the calculated data are already near convergence when only the first solvation shell is explicitly considered. Notice that this synergic effect of explicit/continuum solvation is more evident in the present case than for the vertical excitation energies,⁵⁰ as also noticed elsewhere.²² While a more systematic study of such a topic is necessary in order to better understand the behavior of QM/MM/PCM approaches, we believe that the inclusion of the continuum embedding should always be beneficial, because it provides the correct boundary conditions.

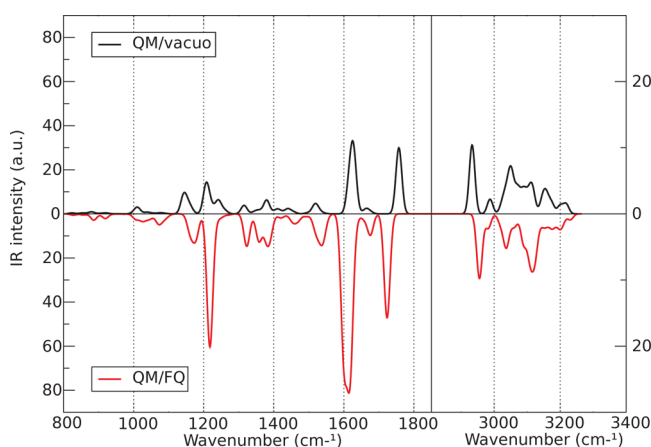
In order to show an application of analytical geometrical first derivatives, we have chosen a system which has already been treated by some of us in a previous work,⁵⁰ i.e., the retinal chromophore in a rhodopsin mimic (see Figure 2).⁷⁶

Figure 3 reports a pictorial view of optimized geometries as calculated by exploiting a hierarchy of models to account for the environment. The QM portion (the retinal) was treated at the B3LYP/6-31G* level, and the MM portion was held fixed. The nonpolarizable QM/MM calculations were performed by using the AMBER⁷⁷ force field and the QEq²⁸ charges. In the QM/FQ calculations, the CHarMM parameters^{41,42} are exploited to define the polarizable electrostatics, and the hardnesses were scaled as suggested in ref 42. PCM calculations were obtained by using the IEFPCM approach⁷⁸ and a dielectric constant set to 15.⁷⁹ The differences between the various models are not negligible; this is also demonstrated by Table 1, where selected bond distances and angles are reported (see Figure 4 for the definition).

Table 2. Harmonic Frequencies (cm^{-1}) and Infrared Intensities (km/mol) of Pyrimidine Computed *in Vacuo* and in Aqueous Solution As Modeled by PCM or QM/MM^a

mode	vacuum		PCM		FQ snapshot		QEq snapshot		$\langle \text{FQ@MD} \rangle$	
	ν	int	ν	int	ν	int	ν	int	ν	int
A1 1	3215	8	3229	4.8	3255	0.0	3230	5.2	3239	2.3
A1 2	3186	15.7	3187	0.0	3194	4.5	3206	1.0	3204	5.3
A1 3	3171	12.8	3182	34.9	3185	20.2	3203	7.9	3177	16.3
A1 4	1614	48.0	1609	53.3	1616	28.6	1615	33.8	1614	36.6
A1 5	1438	58.3	1434	81.4	1443	54.3	1441	56.4	1441	53.6
A1 6	1160	1.0	1155	0.2	1168	0.4	1165	0.3	1164	0.4
A1 7	1077	0.7	1076	0.5	1084	0.0	1082	0.2	1081	0.3
A1 8	1011	3.6	1011	5.0	1018	0.9	1017	5.6	1015	4.2
A1 9	694	3.3	690	3.5	696	1.7	694	2.9	695	2.4
A2 1	992	0.0	999	0.0	1000	0.2	1001	0.2	1003	0.4
A2 2	409	0.0	408	0.0	429	0.0	422	0.0	420	0.1
B1 1	1013	0.0	1017	0.0	1021	5.6	1027	0.2	1024	0.6
B1 2	973	0.0	976	0.0	971	0.3	982	0.1	978	0.1
B1 3	818	5.3	821	5.6	826	2.9	835	4.5	828	5.0
B1 4	733	41.8	731	46.6	736	35.5	739	35.3	740	33.9
B1 5	351	3.6	352	4.1	362	3.2	368	3.1	363	2.9
B2 1	3175	18.8	3188	18.2	3191	1.6	3210	7.7	3191	6.8
B2 2	1613	81.2	1615	118.7	1632	76.1	1625	79.6	1623	71.5
B2 3	1492	6.6	1494	8.3	1502	5.1	1505	6.5	1500	5.7
B2 4	1391	0.2	1393	0.5	1402	0.3	1408	0.5	1400	0.7
B2 5	1261	5.3	1260	4.0	1277	3.1	1274	5.2	1271	4.3
B2 6	1227	8.3	1223	14.2	1236	6.5	1234	8.3	1232	6.9
B2 7	1092	3.4	1093	6.8	1112	5.0	1106	4.6	1103	4.4
B2 8	632	9.9	633	11.3	642	11.6	640	11.4	637	10.3
RMS			5	10.8	14	6.7	15	5.1	10	5.1

^aQM/MM calculations were performed by using the polarizable QM/FQ/PCM model (both the results of a single snapshot or averaged over 70 snapshots— $\langle \text{FQ@MD} \rangle$ —are reported) or the standard QM/MM approach with QEq charges to model the solvent electrostatics. To summarize the results, we also report the RMS solvent shifts for every model.

**Figure 6.** IR spectra of retinal in a rhodopsin mimic as calculated for the isolated molecule and with the QM/FQ approach.

As a last numerical application, we will focus on harmonic IR spectra of a solvated system, i.e., pyrimidine in aqueous solution, and the already discussed retinal in a rhodopsin mimic.

Before presenting any result, a methodological premise is required. In the following, we will adopt the aforementioned Partial Hessian Vibrational Approach (PHVA),^{61–67} where only a portion of the full molecular Hessian is considered. In particular, we will only treat the QM–QM portion of the Hessian matrix, i.e., the one obtained by twice differentiating the energy with respect to the coordinates of nuclei belonging

to the QM-described portion of the system. This is, of course, an approximation. On the other hand, it avoids the consideration of a possibly extremely large number of degrees of freedom, and it is particularly helpful for focused models, where the interest stands in the properties of the solute and not of the system as a whole. We would also like to point out that the results we present are to be considered as proofs of concept and are not meant to be directly compared with experimental observables. A more quantitative validation of the QM/FQ/PCM method has been provided by some of the authors in a previous paper,⁸⁰ where a full QM treatment, possibly coupled to a PCM embedding (QM/QM/PCM), is compared with our QM/FQ/PCM approach and a nonpolarizable QM/MM/PCM one in the case of pyrimidine in aqueous solution, as modeled in terms of a pyrimidine + 2 water molecules cluster. The QM/FQ/PCM most closely reproduces both the QM/QM/PCM IR frequencies and intensities.

Figure 5 reports calculated IR spectra of pyrimidine in the gas phase and in aqueous solution as described by means of the QM/FQ/PCM approach (a list of frequencies and intensities of all modes are given in Table 2). To take into account not only molecular motions but also the slower rearrangement of solvent molecules, the spectrum in solution was obtained as an average over 70 configurations taken from an MD simulation (see ref 73 for details), where the (QM) solute's geometry was optimized while keeping the water molecules fixed. Such an approach allows one to provide statistically meaningful results, as the MD takes care of the averaging over possible solvent configurations. As the two studied phenomena—molecular

vibrations and overall solvent motions—are characterized by different time scales, a mixed classical/quantum treatment offers a reliable description of the problem at a reasonable computational cost. The pyrimidine was described at the B3LYP/N07D level of theory.^{81,82} Intensities in solution were scaled by $1/n$, with n being the refractive index of water.⁸³ For the sake of completeness, in Table 2 we also report the same quantities calculated both with our QM/FQ/PCM model and with a nonpolarizable QM/MM/PCM description, where the MM charges were obtained by means of the QEq²⁸ algorithm, for a single snapshot taken from the MD simulation. The inclusion of environmental effects causes, as expected, a shift in the calculated frequency values, which results in either an increase or a decrease of the values depending on the mode under investigation. The relative band intensities also change and, in general, are more affected by the environment than the corresponding frequencies. In general, all the solvation approaches give consistent results, not only for frequencies but noticeably also for intensities. As expected, the PCM intensities are generally larger than the corresponding values *in vacuo*. The QM/FQ/PCM intensities are generally slightly larger than the corresponding nonpolarizable QM/MM/PCM ones, which is consistent with the introduction of polarization effects.

Finally, Figure 6 shows calculated harmonic IR spectra for retinal either isolated or embedded in a rhodopsin mimic, as modeled by the QM/FQ approach (a list of frequencies and intensities of all modes is given as Supporting Information). In general, the effect of the environment is noticeable and does not simply result in a scaling of the spectrum of the isolated molecule. In general relative intensities are more affected by the environment than frequency values. The bands more affected by the environment are that around 1600 cm⁻¹, due to chain motions, and the one around 1700 cm⁻¹, due to the C=O stretching mode. The latter is shifted by -39 cm⁻¹ with PCM and -34 cm⁻¹ with QM/FQ, whereas the QM/MM approach gives a shift of +6 cm⁻¹. These findings demonstrate the crucial effects due to the introduction of polarization effects.

5. SUMMARY, CONCLUSIONS, AND FUTURE PERSPECTIVES

In this paper, we have reported the analytical formulation and implementation of energy first and second derivatives for a fully polarizable QM/MM Hamiltonian with the possible inclusion of a third layer treated by means of a continuum solvation approach rooted in the PCM. Although there is much interest nowadays in polarizable QM/MM strategies, to the best of our knowledge this contribution shows the first extension of them to analytical first and second derivatives and therefore paves the way to molecular response and spectroscopic properties. The availability of analytical second derivatives makes the extension of our model beyond the double harmonic approximation (i.e., to anharmonic vibrational spectra) straightforward in the second-order vibrational perturbation theory framework, as the needed cubic and quartic force constants are obtained by numerical differentiation. The extension of our model to treat magnetic and mixed electric/magnetic perturbations is currently under investigation in our laboratory.

A. ANALYTICAL SECOND DERIVATIVES: FULL HESSIAN MATRIX

For the sake of completeness, in this appendix the formulas for the full Hessian matrix, i.e. including also the QM/MM and MM/MM blocks, are given. Derivatives with respect to MM atom coordinates will be denoted by the superscripts ξ, η . The QM-MM block of the Hessian can be obtained by differentiating once the forces on the MM portion with respect to the position of a QM nucleus:

$$\mathcal{E}^{(x\xi)}(\mathbf{P}, \mathbf{q}, \lambda) = \frac{\partial \mathcal{E}^\xi}{\partial x} + \frac{\partial \mathcal{E}^\xi}{\partial \mathbf{P}} \frac{\partial \mathbf{P}}{\partial x} + \frac{\partial \mathcal{E}^\xi}{\partial \mathbf{q}} \frac{\partial \mathbf{q}}{\partial x} + \frac{\partial \mathcal{E}^\xi}{\partial \lambda} \frac{\partial \lambda}{\partial x} \quad (23)$$

where the last term vanishes. Substituting \mathcal{E}^ξ with eq 13:

$$\mathcal{E}^{(x\xi)} = \mathbf{q}^\dagger \mathbf{V}^{x\xi}(\mathbf{P}) + \mathbf{q}^\dagger \mathbf{V}^\xi(\mathbf{P}^x) + (\mathbf{J}^\xi \mathbf{q} + \mathbf{V}^\xi(\mathbf{P}))^\dagger \mathbf{q}^x \quad (24)$$

The derivatives of the density matrix and of the FQs can be obtained by solving the CPHF equations described in Section 3: therefore, there is no need to enlarge the CPHF system of equations to calculate the derivatives of the density matrix with respect to the positions of the MM atoms. This is, however, unavoidable when the MM-MM block of the Hessian is to be calculated. By differentiating eq 13 with respect to the position of MM atoms:

$$\mathcal{E}^{(\xi\eta)}(\mathbf{P}, \mathbf{q}, \lambda) = \frac{\partial \mathcal{E}^\xi}{\partial \eta} + \frac{\partial \mathcal{E}^\xi}{\partial \mathbf{P}} \frac{\partial \mathbf{P}}{\partial \eta} + \frac{\partial \mathcal{E}^\xi}{\partial \mathbf{q}} \frac{\partial \mathbf{q}}{\partial \eta} + \frac{\partial \mathcal{E}^\xi}{\partial \lambda} \frac{\partial \lambda}{\partial \eta} \quad (25)$$

The last term vanishes once again; to calculate the derivatives of the charges and the density, a new set of CPHF equations needs to be solved. Differentiation of the Liouville equation (as the overlap does not depend on the positions of the MM atoms, we can work in the MO basis) and projection onto the o-v block gives:

$$\mathbf{F} \mathbf{P}_{ov}^\xi - \mathbf{P}_{ov}^\xi \mathbf{F} = \mathbf{F}_{ov}^\xi$$

The Fock matrix derivatives have no contributions arising from the one- and two-electron matrices, but only from the density and FQs derivatives:

$$F_{ia}^\xi = G_{ia}(\mathbf{P}^\xi) + \mathbf{q}^{\dagger \xi} \mathbf{V}_{ia} + \mathbf{q}^\dagger \mathbf{V}_{ia}^\dagger \quad (26)$$

By differentiating the FQ equations we obtain:

$$\mathbf{D}^\xi \mathbf{q} + \mathbf{D} \mathbf{q}^\xi = -\mathbf{V}^\xi(\mathbf{P}) - \mathbf{V}(\mathbf{P}^\xi) \quad (27)$$

By putting everything together, a Casida-like system of equations is obtained, where the matrices are defined in eq 22 and the right-hand side reads:

$$\mathbf{Q}_{ia}^\eta = -\mathbf{q}^\dagger \mathbf{V}_{ia}^\xi + \mathbf{V}_{ia}^\dagger \mathbf{D}^{-1} (\mathbf{D}^\xi \mathbf{q} + \mathbf{V}^\xi(\mathbf{P})) \quad (28)$$

■ ASSOCIATED CONTENT

Supporting Information

Table of harmonic frequencies and IR intensities of retinal in gas phase and in a Rhodopsin mimic as obtained by using different approaches to treat environmental effects. This material is available free of charge via the Internet <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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