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REGULAR ARTICLE

Using multipole point charge distributions to provide the electrostatic potential in the variational explicit polarization (X-Pol) potential

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Abstract The equations defining the variational explicit polarization (X-Pol) potential introduced in earlier work are modified in the present work so that multipole point charge distributions are used instead of Mulliken charges to polarize the monomers that comprise the system. In addition, when computing the electrostatic interaction between a monomer whose molecular orbitals are being optimized and a monomer whose electron density is being used to polarize the first monomer, the electron densities of both monomers are represented by atom-centered multipole point charge distributions. In the original formulation of the variational X-Pol potential, the continuous electron density of the monomer being optimized interacts with external Mulliken charges, but this corresponds to the monopole truncation in a multipole expansion scheme in the computation of the Fock matrix elements of the given monomer. The formulation of the variational X-Pol potential introduced in this work (which we are calling the "multipole variational X-Pol potential") represents the electron density of the monomer whose wave function is being variationally optimized in the same way that it represents the electron densities of external monomers when computing the Coulomb interactions between them.

Keywords Explicit polarization (X-Pol) · Polarizable force field · Fragment-based molecular orbital method · Atom-based multipole moments

1 Introduction

The explicit polarization (X-Pol) potential [1–5] is a force field that is based on the principles of quantum mechanics, yet is intended to be computationally affordable enough to be used in simulations of large molecules in condensed phases. The X-Pol potential approximates the total energy of a large system as the sum of the electronic energy and the system's nuclear repulsion energy and an empirically parameterized term that accounts for the energy of the exchange and correlation interactions that occur between monomers. The "monomers" may also be called fragments; they can be water molecules, residues of a biopolymer, substrates, cofactors, or any convenient subsystems of the entire system. The focus of this work is to modify the way in which X-Pol treats the electrostatic potential between individual monomers.

In the original formulation [1] of the X-Pol potential, each monomer is embedded in the electrostatic field due to the quantum mechanical charge density of the rest of the system, which is then approximately represented by a set of atom-centered partial charges. The point charges are obtained through a Mulliken population analysis of the electron density (specifically the density matrix) of every monomer in the system. Because the electron density of each monomer ultimately depends on that of all the others, the monomer electron densities must be determined iteratively and self-consistently. In this way, an X-Pol calculation can be described by a "double self-consistent field (SCF)" procedure: one does an "inner SCF" loop to

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optimize the molecular orbitals for each monomer in the system and also does an “outer SCF” loop to converge the total potential energy and electron density of the entire system. The original formulation of the X-Pol potential, however, is not variational, although each monomer electron density was ultimately self-consistent and the total electronic energy generally converged to a single value; that value was not stationary with respect to changes in the orbitals. The double SCF (DSCF) procedure was originally designed for statistical mechanical Monte Carlo simulations in which internuclear forces are not needed, and the difference between the DSCF energy and that obtained from fully variational X-Pol calculations [2] is negligible. To enable efficient molecular dynamics simulations to be carried out using the X-Pol potential, a subsequent paper introduced the variational X-Pol method [2]. The electronic energies obtained using the variational X-Pol potential are stationary such that analytical gradients can be conveniently obtained. In order to gain this advantage, a complication is encountered in the construction of the Fock matrix of each monomer: rather than being polarized simply by the Coulomb potential of the Mulliken charges [6] of the other atoms in the system, the mutual dependence of the Mulliken population charges on the density matrices must be explicitly incorporated. Consequently, the total external potential for each monomer consists of half contributions from the Mulliken charges of the rest of the system, and the other half comes from the electron densities of the other monomers in the system.

The appearance of both the Mulliken representation and the full electron density representation of each monomer’s charge poses a dilemma when parameterizing or evaluating quantum mechanical methods for treating the monomers because the electrostatic properties of the full electron distribution may differ significantly from those of the Mulliken charge distribution, e.g., these representations may have quite different dipole moments. Furthermore, if one uses extended-basis-set ab initio or density functional calculations for the monomers, one encounters the difficulty that Mulliken charges are rather erratic for extended basis sets. In semiempirical methods, one can correct some of the deficiencies of Mulliken charges and of the overall method by scaling or mapping [7, 8]. Alternatively, one can seek a more faithful representation of the electrostatics implicit in the density matrix, and in the present work, we propose a version of the X-Pol potential that eliminates Mulliken charges yet remains variational. There are three main features in the present representation of the external potential: (1) rather than using Mulliken charges to represent the electron density distributions of all other monomers in the system, a multipole distribution of point charges centered on each atom of each monomer is used to represent those electron densities; (2) when computing the Coulomb interactions between the electrons of a given monomer and the multipole distributions representing other monomers, the “neglect of diatomic differential overlap” (NDDO) approximation [9, 10] is made; (3) multipole distributions centered on each atom are used to represent the electron density of the given monomer itself as well as those of the external monomers. These features allow the electrostatics to be treated consistently at various stages of the calculations; also, change (1) could potentially improve the accuracy of (or at least speed the convergence of) the final X-Pol energy, because previous studies [11–13] have shown that, when compared to using atom-centered point charges such as Mulliken, using atom-centered multipole moments generally (a) provides a more accurate representation of a monomer’s electrostatic potential and (b) does not show as great a dependence on the basis set chosen. When one incorporates all three of these changes into the X-Pol potential described in Ref. [2], one is said to be using the multipole variational X-Pol potential.

In Sect. 2, the X-Pol theory is briefly reviewed, and the use of multipole distributions in place of Mulliken charges and the added approximations are described in detail. Section 3 summarizes and discusses the key points of the derivation of the multipole variational X-Pol potential.

2 Theory

2.1 Review of the X-Pol theory

In order to obtain the X-Pol potential energy of a system, one first divides the system into a set of subsystems; these subsystems are called “fragments” or “monomers,” and they may be defined in any way that the user finds convenient: for example, in a protein, one could call each amino acid a monomer, whereas in a solution, each individual solvent and solute molecule could be considered to be a separate monomer. The wave function of the entire system (Ψ) is then assumed to be a Hartree product of individual monomer wave functions (Φ_m); the subscript gives the label of the monomer, and M is the total number of monomers in the system:

$$\Psi = \prod_{m=1}^{M} \Phi_m. \tag{1}$$

Although, in general, the individual monomer wave functions (Φ_m) may be obtained using any desired method of electronic structure theory, for the variational X-Pol potential, they have been assumed so far to be the antisymmetrized product of spin-orbitals ($\psi_i^m(\mathbf{r}, \sigma)$, where $\mathbf{r}$ is the vector containing the three spatial variables, and σ

is the spin variable) which are in turn simply products of a spin function (α or β) and a spatial molecular orbital ($\varphi_i^m(\mathbf{r})$). When these assumptions are made, the X-Pol potential energy of the entire system ($E_{\text{X-Pol}}$) is given by

$$E_{\text{X}-\text{Pol}} = E_{\text{Elec}} + E_{\text{Int,ED}} \tag{2}$$

where E_{Elec} is the electronic plus nuclear repulsion energy of the entire system, and $E_{\text{Int,ED}}$ is an empirical term that accounts for the exchange and correlation interactions that occur between the electrons of different monomers. (Usually, the exchange is dominated by short-range exchange repulsion, and the correlation is dominated by long-range dispersion interactions and medium-range dispersion-like interactions.) For X-Pol calculations published so far [1–5], $E_{\text{Int,ED}}$ is approximated as the sum of Lennard–Jones interactions between atoms in different monomers. Our focus is on the total electronic energy of the system, which is also given in Eq. 2 of Ref. [2] using slightly different notation (in Ref. [2], as explained at the beginning of page 234108/3, a superscript m is omitted on φ_i, and an analogous superscript is omitted on other quantities referring to monomer m or any other monomer n. The present discussion, however, will be clearer if we make the dependence on monomer label explicit, so we specify φ_i as φ_i^m, H_i as H_i^m, etc.):

$$E_{\text{Elec}} = \sum_{m=1}^{M} \left\{ \left[2\sum_{i\in m} H_i^m + \sum_{ij\in m} \left(2J_{ij}^m - K_{ij}^m \right) + E_{\text{Nuc}}^m \right] + \frac{1}{2}\left(2\sum_{i\in m} I_i^m + \sum_{A\in m} L_A^m \right) \right\} \tag{3}$$

Equation 3 assumes that each monomer is a closed-shell singlet and that all MOs are doubly occupied. In Eq. 3 and subsequent equations, the letters m and n will be used to label monomers, the letters i and j will be used to label spatial molecular orbitals, the letters A and B will be used to label atoms, and notation such as "$i \in m$" and "$B \notin m$" should be read "MO i belonging to molecule m" and "atom B not belonging to molecule m", respectively. The individual terms appearing in Eq. 3 are defined in the following paragraphs; throughout all equations given in this work, a superscripted asterisk (*) means "complex conjugate", and atomic units will be used.

H_i^m is the expectation value of the one-electron Hamiltonian operators H^m, where H^m is the sum of the kinetic and electron-nuclear Coulomb attraction energies of electrons and nuclei belonging to monomer m:

$$H_i^m = \int \varphi_i^{m*}(\mathbf{r}) H^m \varphi_i^m(\mathbf{r}) d\mathbf{r} \tag{4}$$

J_{ij}^m is the Coulomb repulsion integral between electrons of monomer m:

$$J_{ij}^m = \int d\mathbf{r}_1 d\mathbf{r}_2 \frac{\varphi_i^{m*}(\mathbf{r}_1)\varphi_j^{m*}(\mathbf{r}_2)\varphi_i^m(\mathbf{r}_1)\varphi_j^m(\mathbf{r}_2)}{|\mathbf{r}_1 - \mathbf{r}_2|} \tag{5}$$

K_{ij}^m is the exchange integral for electrons belonging to monomer m:

$$K_{ij}^m = \int d\mathbf{r}_1 d\mathbf{r}_2 \frac{\varphi_i^{m*}(\mathbf{r}_1)\varphi_j^{m*}(\mathbf{r}_2)\varphi_j^m(\mathbf{r}_1)\varphi_i^m(\mathbf{r}_2)}{|\mathbf{r}_1 - \mathbf{r}_2|} \tag{6}$$

E_{Nuc}^m is the repulsion energy between the nuclei of monomer m and the nuclei of all other monomers in the system:

$$E_{\text{Nuc}}^m = \frac{1}{2} \sum_{n=1}^{M} \sum_{A\in m} \sum_{\substack{B\in n \\ B\neq A}} \frac{Z_A Z_B}{|\mathbf{R}_A - \mathbf{R}_B|} \tag{7}$$

where $\mathbf{R}_A$ is the position of atom A, and Z_A is the effective nuclear charge on atom A. In an all-electron calculation, effective nuclear charge is the same as nuclear charge, but in a valence-electron calculation, it is the nuclear charge minus the number of core electrons. Notice that we treat Z_A as a unitless positive integer; e is the charge on a proton, and it carries the units.

As defined in Ref. [2], I_i^m is an approximation of the interaction energy of the electron density due to the doubly occupied spatial molecular orbital MO i (φ_i) of monomer m under the external potential due to the charge densities of all other monomers in the system (q_B is the Mulliken charge [6] in units of e on atom B, which is *not* a member of molecule m. q_B is defined in Eq. 18 of Ref. [2]; it will be replaced with other terms when we derive the multipole variational X-Pol equations):

$$I_i^m = \sum_{B\notin m} q_B \int d\mathbf{r}_1 \frac{\varphi_i^{m*}(\mathbf{r}_1)\varphi_i^m(\mathbf{r}_1)}{|\mathbf{r}_1 - \mathbf{R}_B|} \tag{8}$$

L_A^m gives the energy of the Coulomb interactions between atom A of molecule m with the Mulliken charges assigned to all other atoms in the system (again, these Mulliken charges will be replaced with other terms in the multipole variational X-Pol potential):

$$L_A^m = \sum_{B\in n\neq m} \frac{Z_A q_B}{|\mathbf{R}_A - \mathbf{R}_B|} \tag{9}$$

Since the Mulliken charges are partitioned from the electron density distribution of the monomer to which they belong, and the MOs of each monomer in turn depend on the Mulliken charges of the other monomers in the system, this makes the determination of the X-Pol potential an iterative procedure: the Mulliken charges of the non-interacting monomers are used to obtain a set of monomer electron densities that are polarized by the Mulliken charges of the other monomers; these polarized monomer electron densities are then used to obtain a new set of Mulliken charges for each monomer, which are then used to obtain new electron densities, and so on until the Mulliken charges and/or the total energy of the system (given in Eq. 3) have/has converged. The multipole variational X-Pol potential, which will be described in Sects. 2.2 through 2.3, replaces each monomer's Mulliken charges with sets of point charges that approximate the monopole and dipole terms in atom-centered multipole expansions of the electrostatic potential due to that monomer's electron density. Two new approximations are introduced for the multipole variational X-Pol potential, and these will be discussed in detail in Sects. 2.2 through 2.3 as well.

2.2 Replacing Mulliken charges and orbital electron densities with multipole distributions in the X-Pol potential

In the X-Pol method, the expression for the total electronic energy is given in Eq. 3 above. This equation involves quantities defined in Eqs. 8 and 9, and previous applications have made use of scaled Mulliken charges to approximate the external potential. Here, we replace both Eqs. 8 and 9 by including the dipole moment term that accounts for the *sp*-type polarizations on non-hydrogen atomic centers. As noted above, the quantity I_i in Eq. 8 gives an approximation to the one- and two-electron Coulomb integrals between MO i (φ_i) of monomer m and the charge densities of all other monomers in the system:

$$I_i^m \approx V_i^m \equiv \sum_{n\neq m} V_{n,i}^m \equiv \sum_{n\neq m}\sum_{B\in n} \int d\mathbf{r}_1 \left\{ \varphi_i^{m*}(\mathbf{r}_1)\varphi_i^m(\mathbf{r}_1)\left[\left(\int d\mathbf{r}_2 \frac{\rho_n(\mathbf{r}_2)}{|\mathbf{r}_1-\mathbf{r}_2|}\right) - \frac{Z_B}{|\mathbf{r}_1-\mathbf{R}_B|}\right]\right\} \tag{10}$$

where $V_{n,i}^m$ is the electrostatic interaction energy between the electron density due to MO i and the charge density of monomer n, which is the sum of the nuclear charge density and the electron density ρ_n of monomer n:

$$\rho_n(\mathbf{r}) = 2\sum_{\substack{j=1\\ j\in n}}^{N_j} \varphi_j^{n*}(\mathbf{r})\varphi_j^n(\mathbf{r}) \tag{11}$$

where N_j is the number of doubly occupied orbitals on monomer j. In Eq. 11, φ_j^n are the MOs of monomer n. Let us now assume that the MOs of each monomer may be expanded in a set of normalized atom-centered basis functions, χ_p^n:

$$\varphi_j^n(\mathbf{r}) = \sum_p \chi_p^n(\mathbf{r})C_{pj}^n \tag{12}$$

We also introduce a density matrix $\mathbf{P}^n$ that is defined by the expansion coefficients of MO j:

$$P_{pq}^n = 2\sum_{j=1}^{N_j} C_{qj}^n C_{pj}^{n*} \tag{13}$$

where the factor of 2 accounts for the double occupancy of each spatial MO. One may then rewrite Eq. 10 as:

$$V_i^m = \sum_{n\neq m}\sum_{pq,B\in n}\int d\mathbf{r}_1\{\varphi_i^{m*}(\mathbf{r}_1)\varphi_i^m(\mathbf{r}_1)\left[P_{pq}^n\left(\int d\mathbf{r}_2\frac{\chi_p^{n*}(\mathbf{r}_2)\chi_q^n(\mathbf{r}_2)}{|\mathbf{r}_1-\mathbf{r}_2|}\right) - \frac{Z_B}{|\mathbf{r}_1-\mathbf{R}_B|}\right]\} \tag{14}$$

The notation can be simplified by introducing the following definitions:

$$V_{\mathrm{B},i}^m \equiv Z_B\int d\mathbf{r}_1\frac{\varphi_i^{m*}(\mathbf{r}_1)\varphi_i^m(\mathbf{r}_1)}{|\mathbf{r}_1-\mathbf{R}_B|} \tag{15}$$

$${}^m\langle ii||pq\rangle^n \equiv \iint d\mathbf{r}_2 d\mathbf{r}_1\frac{\varphi_i^{m*}(\mathbf{r}_1)\varphi_i^m(\mathbf{r}_1)\chi_p^{n*}(\mathbf{r}_2)\chi_q^n(\mathbf{r}_2)}{|\mathbf{r}_1-\mathbf{r}_2|} \tag{16}$$

Equations 10 and 14 may then be written in a much simpler form:

$$V_i^m = \sum_{n\neq m}\left[\sum_{pq\in n}P_{pq}^n\,{}^m\langle ii||pq\rangle^n - \sum_{B\in n}V_{\mathrm{B},i}^m\right] \tag{17}$$

Now, we make the neglect of diatomic differential overlap [9, 10] (NDDO) approximation. This has the effect that if χ_p and χ_q are centered on different atoms, their differential overlap (or, to put it another way, the electron density due to their overlap) $\chi_p^*(\mathbf{r})\chi_q(\mathbf{r})d\mathbf{r}$ is approximated as zero at all points in space (we will write this in a shorthand way as $|pq\rangle \approx 0$).

Next, we introduce the minimum valence basis set approximation. In this approximation, the basis set $\{\chi_p\}$ on each atom is assumed to be a minimal basis consisting of a single s function if the atom is hydrogen and consisting of four functions, s, p_x, p_y, and p_z, if the atom is a p block element, and core electrons are absorbed into the nucleus.

In addition, we employ the Dewar–Thiel approximation [14] of computing the two-electron repulsion integrals (which is used in the MNDO, AM1 [15], and PM3 [10, 16, 17] models). In this treatment (explained in detail in Refs. [14] and [18]), if p and q are centered on the same atom, one can represent the electron density of the product $\chi_p^*\chi_q$ as a set of point charges that yields the monopole, dipole, and quadrupole terms in the multipole expansion of the electrostatic potential due to that electron density.

There is one further simplification in the present treatment. In particular, in treating V_i^m, we neglect the quadrupole contributions. Note, however, that we retain these for the intramonomer terms in Eq. 3 if the NDDO formalism (MNDO, AM1, PM3, etc.) is also being used to obtain the individual monomer wave functions.

Table 1 shows how NDDO theory approximates all possible forms of $\chi_p^*\chi_q$ that can occur on a single atomic center using a minimum valence basis set. This table considers both the intramonomer and intermonomer cases, but in the discussion that follows, we discuss only the intermonomer terms (the intramonomer terms are unchanged from MNDO and are presented in Ref. [14]).

We now introduce another shorthand notation:

$$q^B_{apq} = c_{apq} P^{n(B)}_{pq} \delta_{A(p)A'(q)} \delta_{A(p)B} \tag{18}$$

where $n(B)$ denotes the monomer n that contains atom B, q^B_{apq} is one of the point charges used in the multipole distribution that represents electron density $|pq\rangle$, basis function χ_p is on atom $A(p)$, basis function χ_q is on atom $A'(q)$, and a is an index that ranges from 1 to A_{pq}, where A_{pq} is the number of charges used to represent the multipole distribution associated with electron density $|pq\rangle$ given in Table 1 (for this work, A_{pq} is at most 2). The constant c_{apq} is 1 if a monopole charge distribution is used to represent $|pq\rangle$, whereas it is either ½ or −½ if a dipole distribution is used to represent $|pq\rangle$; furthermore, c_{apq} is zero if χ_p and χ_q are not on the same atom (as enforced by the first kronecker delta in Eq. 18). Table 2 lists the values of c_{apq} associated with every possible electron density $|pq\rangle$ when a minimum valence basis set (as specified above) is used to describe the MOs on monomer n and when the NDDO approximation is invoked. The charge q^B_{apq} will be placed at coordinates $\mathbf{r}^B_{apq}$. If a monopole charge distribution is being used, A_{pq} equals one, and $\mathbf{r}^B_{apq}$ equals the coordinate $\mathbf{r}_B$ of the atom on which basis functions χ_p and χ_q are centered. If a dipole distribution is being used, A_{pq} equals two; $\mathbf{r}^B_{1pq}$ will be a distance D_1 away from $\mathbf{R}_B$, and $\mathbf{r}^B_{2pq}$ will also be a distance D_1 away from $\mathbf{R}_B$ but in the opposite direction. D_1 depends on the principal quantum number and the orbital exponents of basis functions χ_p and χ_q; see Fig. 2 and Eq. 15 of Ref. [18] for further clarification. (Equation 15 of Ref. [18] covers the case of *2s2p* charge distributions, but does not apply to *1s2p* charge distributions; however, the formula for *1s2p* distributions can be derived analogously).

Table 1 NDDO approximations of electron densities due to monatomic differential overlap using a minimum valence basis set (see Ref. [10], pg 19)

Atomic orbitals ($\|pq\rangle$)	Multipole distribution[a]	Number of charges[b]
$\|ss\rangle$	Monopole	1 [1]
$\|sp_x\rangle$	Dipole	2 [2]
$\|sp_y\rangle$	Dipole	2 [2]
$\|sp_z\rangle$	Dipole	2 [2]
$\|p_xp_x\rangle$	Monopole [+ linear quadrupole]	1 [4]
$\|p_xp_y\rangle$	[square quadrupole]	0 [4]
$\|p_xp_z\rangle$	[square quadrupole]	0 [4]
$\|p_yp_y\rangle$	Monopole [+ linear quadrupole]	1 [4]
$\|p_yp_z\rangle$	[square quadrupole]	0 [4]
$\|p_zp_z\rangle$	Monopole [+ linear quadrupole]	1 [4]

[a] The distributions not in brackets are used in both intermomoner and intramomomer terms; those in brackets are used only in intramonomer terms

[b] In this column, the first value is the number of charges used in evaluating the intermonomer term V^m_i (these values are equivalent to A_{pq} for the given pair of basis functions χ_p and χ_q; see text), and value in brackets is the number used in intramonomer terms

Table 2 Values of c_{apq} associated with multipole distribution representations of monatomic differential overlap distributions

$\|pq\rangle$	Index a	c_{apq}
$\|ss\rangle$	1	1
$\|sp_x\rangle$	1	½
$\|sp_x\rangle$	2	−½
$\|sp_y\rangle$	1	½
$\|sp_y\rangle$	2	−½
$\|sp_z\rangle$	1	½
$\|sp_z\rangle$	2	−½
$\|p_xp_x\rangle$	1	1
$\|p_xp_y\rangle$	1	0
$\|p_xp_z\rangle$	1	0
$\|p_yp_y\rangle$	1	1
$\|p_yp_z\rangle$	1	0
$\|p_zp_z\rangle$	1	1

This table assumes that quadrupole interactions are neglected for differential overlap between atoms on separate monomers; Table 3 of the Appendix gives the additional rows that one should add if quadrupole interactions are included (although preliminary studies have indicated that this probably will not be necessary; see footnote *a* of Table 3)

With these approximations and this new notation in hand, we will proceed in two steps. In the first step, we will replace the partial charges on the "MM monomer" n by charge and dipole distributions, and in the second step, we will replace the orbitals of the "QM monomer" m by charge and dipole distributions. ("MM" stands for "molecular mechanics", indicating that this monomer's electron density is represented as a set of point charges, as it would be in a classical MM calculation of the potential energy. "QM" stands for "quantum mechanics", indicating that this monomer's electron density is being allowed to adjust itself in order to yield the minimum potential energy possible in its current environment). At the end of these two steps, the QM and MM monomers will be treated equivalently as far as the intermonomer interaction is concerned.

Unlike MNDO and other NDDO methods, we will calculate the true Coulomb interaction energy between point charge distributions rather than using a damped Coulomb energy formula; this is because we assume that, although charge penetration is likely to occur in intramonomer interactions, it is much less likely to occur in intermonomer interactions. However, in some cases, this assumption may be too severe [19], especially when modeling systems that involve covalently bonded monomers and/or π-π stacking such as DNA [20], and it can be replaced by a more realistic radial interaction without a major change in the formalism.

The first step is to replace the partial charges on the MM monomer n by charge and dipole distributions. To accomplish this, we approximate Eqs. 10, 14, and 17 in the following manner:

$$V_i^m \approx I_i^m = \sum_{n \neq m} \sum_{B \in n} \left[\sum_{pq \in B} \sum_{a=1}^{A_{pq}} q_{apq}^B \int \mathrm{d}\mathbf{r} \frac{\varphi_i^{m*}(\mathbf{r}) \varphi_i^m(\mathbf{r})}{\left| \mathbf{r} - \mathbf{r}_{apq}^B \right|} - V_{B,i} \right] \tag{19}$$

The second step is to replace the orbitals of the QM monomer m by charge and dipole distribution. Note that Eq. 3 involves the quantity

$$I^m = \frac{1}{2} 2 \sum_{i=1}^{N} I_i^m = \sum_{i=1}^{N} I_i^m \tag{20}$$

and it will be preferable to work with I^m rather than just with I_i^m. From Eq. 19, we have

$$I^m = \sum_{i \in m}^{N} \sum_{n \neq m} \sum_{B \in n} \left[-V_{B,i} + \sum_{p'q' \in B} \sum_{a=1}^{A_{p'q'}} q_{ap'q'}^B \int \mathrm{d}\mathbf{r} \frac{\varphi_i^{m*}(\mathbf{r}) \varphi_i^m(\mathbf{r})}{\left| \mathbf{r} - \mathbf{r}_{ap'q'}^B \right|} \right] \tag{21}$$

Using the notation developed above, we have

$$2 \sum_{i \in m}^{N} \varphi_i^{m*}(\mathbf{r}) \varphi_i^m(\mathbf{r}) = \sum_{pq \in m} P_{pq}^m \chi_p^{m*}(\mathbf{r}) \chi_q^m(\mathbf{r}) \tag{22}$$

Then, Eq. 21 becomes

$$I^m = \frac{1}{2} \sum_{pq \in m} P_{pq}^m \int \mathrm{d}\mathbf{r} \chi_p^{m*}(\mathbf{r}) \chi_q^m(\mathbf{r}) \sum_{n \neq m} \sum_{B \in n} \left[-\frac{Z_B}{|\mathbf{r} - \mathbf{R}_B|} + \sum_{p'q' \in B} \sum_{a=1}^{A_{p'q'}} \frac{q_{ap'q'}^B}{\left| \mathbf{r} - \mathbf{r}_{ap'q'}^B \right|} \right] \tag{23}$$

Replacing the overlap densities of monomer m with multipole distributions then yields

$$I^m = \frac{1}{2} \sum_{A \in m} \sum_{pq \in A} \sum_{a=1}^{A_{pq}} q_{apq}^A \sum_{n \neq m} \sum_{B \in n} \left[-\frac{Z_B}{\left| \mathbf{r}_{apq}^A - \mathbf{R}_B \right|} + \sum_{p'q' \in B} \sum_{a'=1}^{A_{p'q'}} \frac{q_{a'p'q'}^B}{\left| \mathbf{r}_{apq}^A - \mathbf{r}_{a'p'q'}^B \right|} \right] \tag{24}$$

Finally, we consider the entire interaction between all pairs of monomers. From Eq. 3, we see that this is given by

$$V \equiv E_{\mathrm{Nuc}}^m + \sum_{m=1}^{M} \left(\mathrm{I}^m + \frac{1}{2} \sum_{A \in m} L_A^m \right) \tag{25}$$

where L_A^m is given in Eq. 9, and E_{Nuc}^m is given in Eq. 7.

As before, we must replace the Mulliken approximation that yields a partial charge, in particular q_A, by a corresponding multipole distribution. Doing this yields, after algebra similar to that in going from Eqs. 10 to 24 above, the following expression for V:

$$\begin{aligned} V = \tfrac{1}{2} \sum_{m=1}^{M} \sum_{\substack{n=1 \\ n \neq m}}^{M} \sum_{A \in m} \sum_{pq \in A} \sum_{a=1}^{A_{pq}} \sum_{B \in n} \sum_{p'q' \in B} \sum_{a'=1}^{A_{p'q'}} \frac{q_{apq}^A q_{a'p'q'}^B}{\left| \mathbf{r}_{apq}^A - \mathbf{r}_{a'p'q'}^B \right|} \\ - \sum_{m=1}^{M} \sum_{\substack{n=1 \\ n \neq m}}^{M} \sum_{A \in m} \sum_{pq \in A} \sum_{a=1}^{A_{pq}} \sum_{B \in n} \frac{q_{apq}^A Z_B}{\left| \mathbf{r}_{apq}^A - \mathbf{R}_B \right|} \\ + \tfrac{1}{2} \sum_{m=1}^{M} \sum_{\substack{n=1 \\ n \neq m}}^{M} \sum_{A \in m} \sum_{B \in n} \frac{Z_A Z_B}{|\mathbf{R}_A - \mathbf{R}_B|} \end{aligned} \tag{26}$$

Our next goal is to derive the variational X-Pol equations using Eq. 26 of this work in place of the sum over m of E_{Nuc}^m and the last row of Eq. 3. In carrying out this derivation, we must notice that q_{apq}^B depends on P_{pq}^n by Eq. 18 above, where n is the monomer that contains atom B.

2.3 Variation of density matrix elements with changes in the variational coefficients

In many electronic structure theories, the wave function of a singlet system is constructed from a product (or antisymmetrized product) of N_i doubly occupied molecular orbitals (MOs), which are functions of the three spatial coordinates $(\mathbf{r})$. Each member of the set of MOs $\{\phi_i(\mathbf{r})\}$ is assumed to be a linear combination of N_{basis} atom-centered basis functions $\{\chi_p(\mathbf{r})\}$:

$$\phi_i(\mathbf{r}) = \sum_{p=1}^{N_{\mathrm{basis}}} \chi_p(\mathbf{r}) C_{pi} \tag{27}$$

Equation 27 is a more general form of Eq. 12, and it may be written in matrix–vector notation as:

$$\phi = \chi \mathbf{C} \tag{28}$$

where ϕ is an N_i-dimensional row vector whose components are the MOs, $\boldsymbol{\chi}$ is an N_{basis}-dimensional row vector whose components are the basis functions, and $\mathbf{C}$ is an $(N_{\mathrm{basis}} \times N_i)$ matrix of the expansion coefficients. We may also define an N_{basis}-dimensional column vector $\mathbf{c}_i$ which is the ith column of $\mathbf{C}$ so that

$$\phi_i = \chi \cdot \mathbf{c}_i \tag{29}$$

We define the elements of density matrix $\mathbf{P}$ in the following way (which is essentially the same as the definition given in Eq. 13):

$$(\mathbf{P})_{pq} = P_{pq} = 2\sum_{i=1}^{N_i} C_{qi} C_{pi}^{*} \tag{30}$$

where, as in Eqs. 12 and 13 above, p and q are indices that denote atom-centered basis functions and i is an index that denotes a molecular orbital. We find that we may write:

$$(\mathbf{P})_{pq} = P_{pq} = 2\sum_{i=1}^{N_i} \sum_{\rho}^{N_{\mathrm{basis}}} \sum_{\sigma}^{N_{\mathrm{basis}}} C_{qi}\delta_{q\sigma}\delta_{p\rho} C_{pi}^{*} \tag{31}$$

If we define the elements of a matrix $\mathbf{T}^{(p,q)}$ in the following way,

$$\left(\mathbf{T}^{(p,q)}\right)_{\rho\sigma} = \delta_{p\rho}\delta_{q\sigma} \tag{32}$$

then we may write:

$$(\mathbf{P})_{pq} = P_{pq} = 2\sum_{i=1}^{N_i} \sum_{\rho}^{N_{\mathrm{basis}}} \sum_{\sigma}^{N_{\mathrm{basis}}} C_{qi}\left(\mathbf{T}^{(p,q)}\right)_{\rho\sigma} C_{pi}^{*} \tag{33}$$

or

$$(\mathbf{P})_{pq} = P_{pq} = 2\sum_{i=1}^{N_i} \mathbf{c}_i^{\dagger}\mathbf{T}^{(p,q)}\mathbf{c}_i \tag{34}$$

(Notice that the $\mathbf{T}^{(p,q)}$ matrix is simply a matrix where the (p,q)th element is 1 and where all other elements are 0). The superscript "†" means "adjoint" or "complex conjugate of the transpose".

For the multipole variational X-Pol method, we will need to know how each matrix element P_{pq} varies with an infinitesimal change in the $\mathbf{c}_i$ ($\delta\mathbf{c}_i$). We simply use the product rule to find:

$$\delta P_{pq} = 2\sum_{i=1}^{N_i}\left[\delta\mathbf{c}_i^{\dagger}\mathbf{T}^{(p,q)}\mathbf{c}_i + \mathbf{c}_i^{\dagger}\mathbf{T}^{(p,q)}\delta\mathbf{c}_i\right] \tag{35}$$

2.4 Variation of the electronic energy with changes in the variational coefficients

In the multipole variational X-Pol method, point charges are used to represent multipole moments of the differential overlap between two basis functions centered on the same atom. If q_{apq}^{A} is the a^{th} point charge in the set of point charges representing the monopole and dipole terms of the electrostatic potential due to electron density $|pq\rangle$ centered on atom A, then we write

$$q_{apq}^{A} = c_{apq} P_{pq}^{m(A)} \delta_{A(p)A'(q)} \delta_{A(p)B} \tag{36}$$

as explained in Sect. 2.2. Because the only term in Eq. 36 that depends on $\mathbf{c}_i$ is $P_{pq}^{m(A)}$,, we find that the variation in the multipole point charges is:

$$\begin{aligned} \delta q_{apq}^{A} &= c_{apq}\,\delta P_{pq}^{m(A)} \delta_{A(p)A'(q)} \delta_{A(p)B} \\ &= 2c_{apq}\sum_{i=1}^{N_i}\left[\delta\left(\mathbf{c}_i^{m}\right)^{\dagger}\mathbf{T}^{(p,q)}\mathbf{c}_i^{m} + \left(\mathbf{c}_i^{m}\right)^{\dagger}\mathbf{T}^{(p,q)}\delta\mathbf{c}_i^{m}\right] \\ &\quad \delta_{A(p)A'(q)}\delta_{A(p)B} \end{aligned} \tag{37}$$

We take variations with respect to the coefficients of MOs on each molecule m, so the variation in V is given by:

$$\begin{aligned} \delta V = &\sum_{m=1}^{M}\sum_{\substack{n=1\\ n\neq m}}^{M}\sum_{A\in m}\sum_{pq\in A}\sum_{a=1}^{A_{pq}}\sum_{B\in n}\sum_{p'q'\in B}\sum_{a'=1}^{A_{p'q'}}\frac{\delta q_{apq}^{A} q_{a'p'q'}^{B}}{\left|\mathbf{r}_{apq}^{A} - \mathbf{r}_{a'p'q'}^{B}\right|} \\ &- \sum_{m=1}^{M}\sum_{\substack{n=1\\ n\neq m}}^{M}\sum_{A\in m}\sum_{pq\in A}\sum_{a=1}^{A_{pq}}\sum_{B\in n}\frac{\delta q_{apq}^{A} Z_B}{\left|\mathbf{r}_{apq}^{A} - \mathbf{R}_B\right|} \end{aligned} \tag{38}$$

The variation in V in terms of variations in the expansion coefficients is given in Eq. 39 below.

$$\begin{aligned} \delta V = &\sum_{m=1}^{M}\sum_{\substack{i=1\\ i\in m}}^{N_i}\sum_{\substack{n=1\\ n\neq m}}^{M}\sum_{A\in m}\sum_{pq\in A}\sum_{a=1}^{A_{pq}}\sum_{B\in n}\sum_{p'q'\in B}\sum_{a'=1}^{A_{p'q'}}\frac{2c_{apq}q_{a'p'q'}^{B}\left[\delta\left(\mathbf{c}_i^{m}\right)^{\dagger}\mathbf{T}^{(p,q)}\mathbf{c}_i^{m} + \left(\mathbf{c}_i^{m}\right)^{\dagger}\mathbf{T}^{(p,q)}\delta\mathbf{c}_i^{m}\right]\delta_{A(p)A'(q)}\delta_{A(p)B}}{\left|\mathbf{r}_{apq}^{A} - \mathbf{r}_{a'p'q'}^{B}\right|} \\ &- \sum_{m=1}^{M}\sum_{\substack{i=1\\ i\in m}}^{N_i}\sum_{\substack{n=1\\ n\neq m}}^{M}\sum_{A\in m}\sum_{pq\in A}\sum_{a=1}^{A_{pq}}\sum_{B\in n}\frac{2Z_B c_{apq}\left[\delta\left(\mathbf{c}_i^{m}\right)^{\dagger}\mathbf{T}^{(p,q)}\mathbf{c}_i^{m}+\left(\mathbf{c}_i^{m}\right)^{\dagger}\mathbf{T}^{(p,q)}\delta\mathbf{c}_i^{m}\right]\delta_{A(p)A'(q)}\delta_{A(p)B}}{\left|\mathbf{r}_{apq}^{A}-\mathbf{R}_B\right|} \end{aligned} \tag{39}$$

Now that we know the variation in V due to variations in $\mathbf{c}_i^m$, we seek the variation in the total electronic energy of the entire system (E_{Elec}). After substituting V for sum over m of E_{Nuc}^m and the final row of Eq. 3, we have:

$$E_{\mathrm{Elec}} = \sum_{m=1}^{M} \left[2 \sum_{i \in m} H_i^m + \sum_{ij \in m} \left(2J_{ij}^m - K_{ij}^m \right) \right] + V \tag{40}$$

From Eq. 40 and from the reasoning in Eqs. 27 through 35 of this work, we may write:

$$\begin{aligned} \delta E_{\mathrm{Elec}} = &\sum_{m=1}^{M} 2 \sum_{i \in m} \delta\left(\mathbf{c}_i^m\right)^{\dagger} \left[\mathbf{H} + \sum_{j \in m} \left(2\mathbf{J}_j - \mathbf{K}_j\right) \right] \mathbf{c}_i^m \\ &+ \sum_{m=1}^{M} 2 \sum_{i \in m} \left(\mathbf{c}_i^m\right)^{\dagger} \left[\mathbf{H} + \sum_{j \in m} \left(2\mathbf{J}_j - \mathbf{K}_j\right) \right] \delta \mathbf{c}_i^m + \delta V \end{aligned} \tag{41}$$

where the operators $\mathbf{H}$, $\mathbf{J}_j$, and $\mathbf{K}_j$ are defined by their relationships to matrix elements H_i^m, J_{ij}^m, and K_{ij}^m through the MO coefficient vectors $\mathbf{c}_i^m$:

$$H_i^m = \left(\mathbf{c}_i^m\right)^{\dagger} \mathbf{H} \mathbf{c}_i^m \tag{42}$$

$$J_{ij}^m = \left(\mathbf{c}_i^m\right)^{\dagger} \mathbf{J}_j \mathbf{c}_i^m = \left(\mathbf{c}_j^m\right) \mathbf{J}_i \mathbf{c}_j^m \tag{43}$$

$$K_{ij}^m = \left(\mathbf{c}_i^m\right)^{\dagger} \mathbf{K}_j \mathbf{c}_i^m = \left(\mathbf{c}_j^m\right) \mathbf{K}_i \mathbf{c}_j^m \tag{44}$$

Notice from Eqs. 5 and 6 that the operators $\mathbf{J}_i$ and $\mathbf{K}_i$ depend on the complete set of coefficients that define MO j of monomer m: $\mathbf{c}_j^m$. Taking variations in matrix elements J_{ij}^m and K_{ij}^m with respect to both $\mathbf{c}_i^m$ and $\mathbf{c}_j^m$ and then summing over both i and j has the same effect as simply taking variations with respect to $\mathbf{c}_i^m$, summing over both i and j, and then doubling the result. This explains why a factor of two appears before the sum over i in Eq. 41. See Sect. 2 of Ref. [21] for a more detailed explanation.

Because the operators $\mathbf{H}$, $\mathbf{J}_j$ $\mathbf{K}_j$, and $\mathbf{T}^{(p,q)}$ are Hermitian, we may write:

$$\begin{aligned} \delta E_{\mathrm{Elec}} = &\sum_{m=1}^{M} 2 \sum_{i \in m} \delta\left(\mathbf{c}_i^m\right)^{\dagger} \Bigg\{ \mathbf{H} + \sum_{j \in m} \left(2\mathbf{J}_j - \mathbf{K}_j\right) \\ &+ \sum_{\substack{n=1 \\ n \neq m}}^{M} \sum_{A \in m} \sum_{pq \in A} \sum_{a=1}^{A_{pq}} \sum_{B \in n} c_{apq} \delta_{A(p)A'(q)} \delta_{A(p)B} \\ &+ \left[\left(\sum_{p'q' \in B} \sum_{a'=1}^{A_{p'q'}} \frac{q_{a'p'q'}^B}{\left| \mathbf{r}_{apq}^A - \mathbf{r}_{a'p'q'}^B \right|} \right) - \frac{Z_B}{\left| \mathbf{r}_{apq}^A - \mathbf{R}_B \right|} \right] \mathbf{T}^{(p,q)} \Bigg\} \mathbf{c}_i^m \\ &+ \sum_{m=1}^{M} 2 \sum_{i \in m} \delta\left(\mathbf{c}_i^m\right)^{T} \Bigg\{ \mathbf{H}^* + \sum_{j \in m} \left(2\mathbf{J}_j^* - \mathbf{K}_j^*\right) \\ &+ \sum_{\substack{n=1 \\ n \neq m}}^{M} \sum_{A \in m} \sum_{pq \in A} \sum_{a=1}^{A_{pq}} \sum_{B \in n} c_{apq} \delta_{A(p)A'(q)} \delta_{A(p)B} \\ &\times \left[\left(\sum_{p'q' \in B} \sum_{a'=1}^{A_{p'q'}} \frac{q_{a'p'q'}^B}{\left| \mathbf{r}_{apq}^A - \mathbf{r}_{a'p'q'}^B \right|} \right) - \frac{Z_B}{\left| \mathbf{r}_{apq}^A - \mathbf{R}_B \right|} \right] \mathbf{T}^{(p,q)*} \Bigg\} \mathbf{c}_i^{m*} \end{aligned} \tag{45}$$

where superscript T means "transpose". (In going from Eqs. 41 to 45, we have used the identity $\mathbf{x}\hat{\mathbf{A}}\mathbf{y} = \mathbf{y}^T\hat{\mathbf{A}}^*\mathbf{x}^*$, where $\mathbf{x}$ and $\mathbf{y}$ are vectors belonging to the same vector space and $\hat{\mathbf{A}}$ is a Hermitian operator that acts on vectors in that vector space.)

Let us call everything in curly braces in Eq. 45 our Fock operator for molecule m ($\mathbf{F}^m$); that is,

$$\begin{aligned} \mathbf{F}^m = &\mathbf{H} + \sum_{j \in m} \left(2\mathbf{J}_j - \mathbf{K}_j\right) + \sum_{\substack{n=1 \\ n \neq m}}^{M} \sum_{A \in m} \sum_{pq \in A} \sum_{a=1}^{A_{pq}} \sum_{B \in n} c_{apq} \\ &\delta_{A(p)A'(q)} \delta_{A(p)B} \left[\left(\sum_{p'q' \in B} \sum_{a'=1}^{A_{p'q'}} \frac{q_{a'p'q'}^B}{\left| \mathbf{r}_{apq}^A - \mathbf{r}_{a'p'q'}^B \right|} \right) - \frac{Z_B}{\left| \mathbf{r}_{apq}^A - \mathbf{R}_B \right|} \right] \mathbf{T}^{(p,q)} \end{aligned} \tag{46}$$

Now we have:

$$\delta E_{\mathrm{Elec}} = \sum_{m=1}^{M} 2 \sum_{i \in m} \left[\delta\left(\mathbf{c}_i^m\right)^{\dagger} \mathbf{F}^m \mathbf{c}_i^m + \delta\left(\mathbf{c}_i^m\right)^{T} \mathbf{F}^{m*} \mathbf{c}_i^{m*} \right] \tag{47}$$

We seek the set of $\mathbf{c}_i^m$ that minimizes E_{Elec},, but we have a constraint: the final MOs on each monomer must be orthonormal; that is,

$$\left(\mathbf{c}_i^m\right)^{\dagger} \mathbf{S}^m \mathbf{c}_j^m = \delta_{ij} \tag{48}$$

where δ_{ij} is a kroenecker delta and $\mathbf{S}^m$ is the overlap matrix for the basis functions centered on atoms in molecule m:

$$\left(\mathbf{S}^m\right)_{pq} = \int \mathrm{d}\mathbf{r} \chi_p^*(\mathbf{r}) \chi_q(\mathbf{r}) \tag{49}$$

Taking the variation of Eq. 48 with respect to variations in the $\mathbf{c}_i^m$ yields:

$$\delta\left(\mathbf{c}_i^m\right)^{\dagger} \mathbf{S}^m \mathbf{c}_j^m + \left(\mathbf{c}_i^m\right)^{\dagger} \mathbf{S}^m \delta \mathbf{c}_j^m = 0 \tag{50}$$

or, because $\mathbf{S}^m$ is Hermitian,

$$\delta\left(\mathbf{c}_i^m\right)^{\dagger} \mathbf{S}^m \mathbf{c}_j^m + \delta\left(\mathbf{c}_j^m\right)^{T} \mathbf{S}^{m*} \mathbf{c}_i^{m*} = 0 \tag{51}$$

We multiply the restriction given in Eq. 51 by a Lagrangian multiplier $-2\varepsilon_{ij}^m$ and sum together all of the resulting restrictions:

$$\sum_{ij \in m} -\delta\left(\mathbf{c}_i^m\right)^{\dagger} \mathbf{S}^m \mathbf{c}_j^m 2\varepsilon_{ij}^m - \delta\left(\mathbf{c}_j^m\right)^{T} \mathbf{S}^{m*} \mathbf{c}_i^{m*} 2\varepsilon_{ij}^m = 0 \tag{52}$$

Notice that

$$\begin{aligned}\delta\left(\mathbf{c}_j^m\right)^T\mathbf{S}^{m*}\mathbf{c}_i^{m*} &= \sum_{pq}\delta C_{pj}C_{qi}^*\int \mathrm{d}\mathbf{r}\chi_p(\mathbf{r})\chi_q^*(\mathbf{r}) \\ &= \int \mathrm{d}\mathbf{r}\left(\sum_p \delta C_{pj}\chi_p(\mathbf{r})\right)\left(\sum_q C_{qi}^*\chi_q^*(\mathbf{r})\right) \\ &= \int \mathrm{d}\mathbf{r}\delta\phi_j(\mathbf{r})\phi_i^*(\mathbf{r}) \end{aligned} \tag{53}$$

Thus, Eq. 52 may be written:

$$-\sum_{ij\in m}\int \mathrm{d}\mathbf{r}\delta\phi_i^*(\mathbf{r})\phi_j(\mathbf{r})2\varepsilon_{ij}^m - \sum_{ij\in m}\int \mathrm{d}\mathbf{r}\delta\phi_j(\mathbf{r})\phi_i^*(\mathbf{r})2\varepsilon_{ij}^m = 0 \tag{54}$$

When we take the sum over all i and j belonging to fragment m, we may switch the order of the indices without changing the value of the sum, so Eq. 52 could just as well be written:

$$-\sum_{ij\in m}\int \mathrm{d}\mathbf{r}\delta\phi_i^*(\mathbf{r})\phi_j(\mathbf{r})2\varepsilon_{ij}^m - \sum_{ij\in m}\int \mathrm{d}\mathbf{r}\delta\phi_i(\mathbf{r})\phi_j^*(\mathbf{r})2\varepsilon_{ji}^m = 0 \tag{55}$$

One may then write Eq. 52 in the following way:

$$\sum_{ij\in m} -\delta\left(\mathbf{c}_i^m\right)^\dagger\mathbf{S}^m\mathbf{c}_j^m 2\varepsilon_{ij}^m - \delta\left(\mathbf{c}_i^m\right)^T\mathbf{S}^{m*}\mathbf{c}_j^{m*}2\varepsilon_{ji}^m = 0 \tag{56}$$

One can show [21] that $\varepsilon_{ji}^m = \varepsilon_{ij}^{m*}$, so if we add the equivalent of zero given in Eq. 56 to the variation in electronic energy given in Eq. 47, we obtain:

$$\begin{aligned}\delta E_{\mathrm{Elec}} = &\sum_{m=1}^{M} 2\sum_{i\in m}\delta\left(\mathbf{c}_i^m\right)^\dagger\left[\mathbf{F}^m\mathbf{c}_i^m - \sum_{j\in m}\mathbf{S}^m\mathbf{c}_j^m\varepsilon_{ij}^m\right] \\ &+ \sum_{m=1}^{M} 2\sum_{i\in m}\delta\left(\mathbf{c}_i^m\right)^T\left[\mathbf{F}^{m*}\mathbf{c}_i^{m*} - \sum_{j\in m}\mathbf{S}^{m*}\mathbf{c}_j^{m*}\varepsilon_{ij}^{m*}\right]\end{aligned} \tag{57}$$

We set $\delta E_{\mathrm{Elec}} = 0$ in order to locate a stationary point (hopefully the minimum) of the electronic energy in the space of the MO coefficients on each monomer. Because the variations $\delta\left(\mathbf{c}_i^m\right)$ are arbitrary, this means that each of their coefficients in Eq. 57 must be equal to zero:

$$\left[\mathbf{F}^m\mathbf{c}_i^m - \sum_{j\in m}\mathbf{S}^m\mathbf{c}_j^m\varepsilon_{ij}^m\right] = 0 \tag{58}$$

$$\left[\mathbf{F}^{m*}\mathbf{c}_i^{m*} - \sum_{j\in m}\mathbf{S}^{m*}\mathbf{c}_j^{m*}\varepsilon_{ij}^{m*}\right] = 0 \tag{59}$$

We see that Eqs. 58 and 59 are equivalent, because Eq. 59 is simply the complex conjugate of Eq. 58. If $\mathbf{E}^m$ is the matrix composed of elements ε_{ij} for molecule m, we may write the requirements given in Eqs. 58 and 59 concisely as the matrix equation:

$$\mathbf{F}^m\mathbf{C}^m = \mathbf{S}^m\mathbf{C}^m\mathbf{E}^m \tag{60}$$

Thus, we see that the set of expansion coefficients that minimizes the multipole variational X-Pol electronic energy is found by self-consistently solving the Roothaan equations [21] for each monomer in the system where the individual monomer Fock operators are defined in Eq. 46.

3 Summary and discussion

Because the variational X-Pol potential in [2] treated the electrostatics of a given monomer differently at different stages of the double SCF process, the variational X-Pol Fock matrix contains terms that give the impression that the monomer's wave is partially polarized by the surrounding Mulliken charges and partially polarized by the full electron densities of the other monomers in the system, even though the term that involves the full electron densities is really consequence of making the total X-Pol energy variational when each monomer is polarized by the surrounding Mulliken charges. To remove this complication from the variational X-Pol potential, one must treat all monomer–monomer interactions "symmetrically": the continuous electron density of the "QM monomer" (i.e., the monomer that on which an "inner SCF" is being performed to optimize its molecular orbitals) must interact with the continuous electron densities of the "MM monomers" (i.e., all other monomers in the system; those whose MOs are not being variationally optimized). This is equivalent to computing all two-electron Coulomb integrals between different fragments. Because the X-Pol potential is intended for use in simulations involving large molecules and/or a large number of small molecules, the less computationally demanding method is preferred. Therefore, to determine the multipole variational X-Pol potential energy of a given system, the electrostatic interactions between the QM monomer and the MM monomers are computed using the Dewar-Thiel approximation with discrete charge–charge interactions. Rather than using a single Mulliken charge to represent the charge density surrounding each atom of each monomer, however, a distribution of point charges is used to represent the electron density surrounding each atom of each monomer.

The way in which the point charge distributions for the multipole variational X-Pol potential can be obtained is summarized below:

1. Assume that only a minimum valence basis set is centered on each atom of each monomer; that is, use only valence *s* and *p* basis functions to describe each atom when calculating "QM monomer–MM monomer (QM/MM)" interaction energies.
2. Assume that diatomic differential overlap may be neglected; that is, for all two-electron integrals that represent the Coulomb interaction between two-electron densities (each arising from the product of two basis functions such as in Eq. 16), assume that the electron densities arising from basis functions centered on different atoms are vanishingly small everywhere in space, making any Coulomb integral involving that electron density essentially zero.
3. Represent all electron densities arising from a pair of valence basis functions centered on the same atom with a distribution of point charges that approximates the monopole and dipole contributions to a multipole expansion of the electrostatic potential due to that electron density. Use the MNDO methodology [14, 18] to determine the locations of the point charges in the multipole distribution around the given atom; use the density matrix element corresponding to the given pair of basis functions to determine the magnitudes of the point charges.

Once the magnitudes and locations of the point charges in multipole distributions have been determined, one can calculate the Coulomb potential between the point charge distributions of the QM monomer and those of the MM monomers as an approximation of the Coulomb interaction energy between the overall electron densities of those monomers.

When calculating the variationally optimal energy and electron density of each monomer in a large system, the multipole variational X-Pol potential approximates the electron density of the QM monomer in the same way in which it approximates the MM monomer electron densities. In so doing, the multipole variational X-Pol potential eliminates a complication that arose in the original formulation of the variational X-Pol method without losing the advantage of yielding a variationally optimized potential energy and wave function (or electron density) of the entire system.

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Appendix

See Appendix Table 3.

Table 3 Additional values of c_{apq} associated with multipole distribution representations of monatomic differential overlap distributions when interfragment quadrupole interactions are included

$\lvert pq\rangle$	Index *a*	c_{apq}
$\lvert p_xp_x\rangle$	2	−½
$\lvert p_xp_x\rangle$	3	¼
$\lvert p_xp_x\rangle$	4	−¼
$\lvert p_xp_y\rangle$	1	¼
$\lvert p_xp_y\rangle$	2	¼
$\lvert p_xp_y\rangle$	3	−¼
$\lvert p_xp_y\rangle$	4	−¼
$\lvert p_xp_z\rangle$	1	¼
$\lvert p_xp_z\rangle$	2	¼
$\lvert p_xp_z\rangle$	3	−¼
$\lvert p_xp_z\rangle$	4	−¼
$\lvert p_yp_y\rangle$	2	−½
$\lvert p_yp_y\rangle$	3	¼
$\lvert p_yp_y\rangle$	4	−¼
$\lvert p_yp_z\rangle$	1	¼
$\lvert p_yp_z\rangle$	2	¼
$\lvert p_yp_z\rangle$	3	−¼
$\lvert p_yp_z\rangle$	4	−¼
$\lvert p_zp_z\rangle$	2	−½
$\lvert p_zp_z\rangle$	3	¼
$\lvert p_zp_z\rangle$	4	−¼

Including intermonomer quadrupole interactions will probably not be necessary in most cases. A study of 27 water dimers (10 of which were stationary points on the potential energy surface) showed that the sum of the quadrupole interactions consistently made up less than 0.5% of the total damped Coulomb interaction energy between the multipole charge distributions centered on the two oxygen atoms of each water dimer tested

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