Beyond isotropic repulsion: Classical anisotropic repulsion by inclusion of \( p \) orbitals

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ABSTRACT

Accurate modeling of intermolecular repulsion is an integral component in force field development. Although repulsion can be explicitly calculated by applying the Pauli exclusion principle, this approach is computationally viable only for systems of limited sizes. Instead, it has previously been shown that repulsion can be reformulated in a “classical” picture: the Pauli exclusion principle prohibits electrons from occupying the same state, leading to a depletion of electronic charge between atoms, giving rise to an enhanced nuclear–nuclear electrostatic repulsion. This classical picture is called the isotropic \( S^2/R \) approximation, where \( S \) is the overlap and \( R \) is the interatomic distance. This approximation accurately captures the repulsion of isotropic atoms such as noble gas dimers; however, a key deficiency is that it fails to capture the angular dependence of the repulsion of anisotropic molecules. To include directionality, the wave function must at least be a linear combination of \( s \) and \( p \) orbitals. We derive a new anisotropic \( S^2/R \) repulsion model through the inclusion of the anisotropic \( p \) orbital term in the total wave function. Because repulsion is pairwise and decays rapidly, it can be truncated at a short range, making it amenable for efficient calculation of energy and forces in complex biomolecular systems. We present a parameterization of the \( 5101 \) dimer database against the \( \text{ab initio} \) benchmark symmetry-adapted perturbation theory, which yields an rms error of only 0.9 kcal/mol. The importance of the anisotropic term is demonstrated through angular scans of water–water dimers and dimers involving halobenzene. Simulation of liquid water shows that the model can be computed efficiently for realistic system sizes.

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I. INTRODUCTION

While it is possible to fully characterize intermolecular interactions through quantum mechanical (QM) calculations, this \( \text{ab initio} \) approach becomes prohibitively expensive for complex systems. Instead, classical force fields can be utilized as an accurate approximation of QM to model intermolecular interactions. Before we proceed, we must note that no force field captures the full complexities of QM. However, a carefully constructed and physics-motivated derivation of the force field terms allows the opportunity to accurately model the QM reality.

Modern efforts are aimed at closing the gap in accuracy between QM and force field calculations. Energy decomposition analyses (EDA), such as symmetry-adapted perturbation theory (SAPT)\(^1\,^2\) and absolutely localized molecular orbitals (ALMO),\(^3\) utilize the perturbation theory to expand the intermolecular energy in four terms: repulsion, electrostatics, induction, and dispersion.\(^4\,^5\) Rigorous physics-based classical force fields should aim to fit to these terms separately.\(^6\) Ideally, computation must be fast, and parameters need to be transferable. Most modern force fields have one concept in common, which is that electrons must be represented as a cloud. While the first-generation force fields treated atoms as point particles, modern force fields incorporate the concept of the electron cloud through either explicit wave functions or semi-empirical hydrogen-like wave functions.\(^7\) The incorporation of the electron cloud gives rise to improved accuracy, such as the “charge penetration” term in electrostatic,\(^8\,^9\) induction,\(^10\,11\) and dispersion.\(^12\) Several next-generation force fields that utilize this first-principles based approaches include AMOEBA+,\(^13\,14\) effective fragment potential (EFP),\(^16\,20\) Gaussian electrostatic model
(GEM),6,21–25 Hydrogen-like Intermolecular Polarizable Potential (HIPPO),10 MB-UCB,11–16 NEMO,17–20 sum of interactions between fragments (SIBFA),21,22 and X-Pol.23–35

Similar to the charge penetration effect above, the electron cloud concept can also be used to derive a model of repulsion. This is precisely what we will do in this paper, but before introducing our new model, we briefly review previous repulsion models to give background and context to our derivation. We introduce four classes of repulsion functions, which are the polynomial, exponential, density overlap, and orbital overlap models, and explain why we chose to use the orbital overlap picture as a starting point of the anisotropic repulsion model.

The first class of repulsion is the polynomial type. This class includes the Lennard-Jones (LJ) 12-6 potential,46 developed in 1924, where repulsion and dispersion is combined by adding the r\(^{-12}\) and r\(^{-6}\) terms. While r\(^{-6}\) dispersion is obtained from the perturbation theory, r\(^{-12}\) repulsion is empirically derived. Another similar model is the buffered 14-7 potential,37 where Halgren introduced empirical buffering constants to fix the overly repulsive nature of the r\(^{-12}\) wall in the LJ model. Although both lack in theoretical justification, the LJ4,39 and buffered 14-7 potentials38,40–42 have been employed with some success. The second class of repulsion is the exponential type, P(r)e\(^{-ar}\), where P(r) is a polynomial.43 After Slater initially proposed this term in 1928, Born, Mayer, and Buckingham later simplified the polynomial as a constant, obtaining A e\(^{-ar}\).44,45 Although successful for hydrocarbons and simple organics,40–42 the isotropic nature of the model fails to capture the angular dependence of repulsion. The third class of repulsion functions is based on density overlap. Inspired by experimental evidence that repulsion is proportional to the overlap of electron densities,46,50–52 Wheatley and Price developed an anisotropic density overlap repulsion model.53 This model is the basis of the Gaussian electrostatic model6,21–23 and recent force fields developed by Van Vleet et al.24–34

This leads us to the final class of repulsion function, which is based on orbital overlap.55 Salem used the Hellmann–Feynman theorem to derive repulsion energy for the helium dimer as ZA S2.56,57 He described repulsion in the classical picture, where the exclusion principle prohibits electrons from occupying the same state, leading to the depletion of electronic charge between atoms and resulting in enhanced nuclear–nuclear electrostatic repulsion. Subsequently, three force fields have adopted Salem’s repulsion based on orbital overlap: the effective fragment potential (EFP), sum of interactions between fragments (SIBFA), and Hydrogen-like Intermolecular Polarizable Potential (HIPPO). EFP uses localized molecular orbitals to calculate the overlap integral, which leads to an accurate and transferable, yet expensive, model for large systems.21,22 SIBFA computes the repulsion between atom centers, bond centers, and lone pairs.29,30,41 HIPPO uses the electrostatic multipoles to extend beyond isotropic repulsion.

Having introduced the relevant previous models, we propose a new repulsion model, which is an extension of the orbital overlap repulsion as described above. Our approach builds upon HIPPO’s isotropic version of the repulsion function, represented as ER = ZA S2 ZB, where Z is the charge parameter, S is the overlap, and R is the interatomic distance. A derivation of this expression will be given in the following section. Intuitively speaking, the equation states that repulsion energy increases by (1) increased overlap between two atoms, (2) decreased interatomic distance, and (3) increased charge parameter. However, the similarity ends as we consider anisotropy. To incorporate the higher order multipoles, HIPPO calculates the gradient of S\(^2\). For instance, when including dipoles, the repulsion term becomes ER = ZA S2 ZB + ZA α\(\nabla\alpha\) \(\nabla\alpha\) ZB, where μ is the dipole. One shortcoming of this model is that the “multipole” expansion deviates from the electrostatic expansion concept. If the interaction operator S\(^2\) were truly electrostatic, the gradient of the operator should be considered, resulting in repulsion expressed as ER = ZA S2 ZB + ZA α\(\nabla\alpha\) ZB. Although the latter formulation is physically valid, it was subsequently found to inadequately fit the water and small molecule dataset. The inclusion of the S\(^2\) term in the gradient introduced extreme angular dependence near equilibrium distances. Curiously, the original model, where the gradient only includes S\(^2\), outperforms the latter model that includes S\(^2\) for reasons yet to be understood.

In this paper, we derive a new model that incorporates anisotropy by including p orbitals in the wave function. In the original HIPPO model, the overlap integral was determined using hydrogen-like s orbitals, and anisotropy was implemented through gradient computations (as described above). In this new model, however, the overlap includes s and p orbital terms, thereby inherently incorporating anisotropy. This eliminates the ambiguity described above, i.e., whether the gradient should apply to the S\(^2\) term when considering higher order multipoles because the multipoles are already accounted for in the overlap S. We simply use the repulsion equation, ER = ZA S2 ZB, which is presented in the theory section following the derivations from Salem, Stone, and Rackers. Subsequently, we introduce p orbitals in the one-electron wave function to accurately capture anisotropic effects. In Sec. IV, we present a parameterization of the S101 dimer database against the SAPT benchmark, which yields an rms error of only 0.9 kcal/mol. We examine molecules beyond the test set and demonstrate the importance of the anisotropic term through angular scans of water–water dimers and of dimers involving halobenzenes. The central processing unit (CPU) and graphics processing unit (GPU) timings show that the novel repulsion function can be computed efficiently for moderate sized systems.

II. THEORY

In this section, the new anisotropic exchange-repulsion model will be derived. In part A, we follow the studies by Salem,56 Stone,60 and Rackers and Ponder,55 to derive isotropic repulsion. In this derivation, the Pauli exclusion principle prohibits two electrons from occupying identical states. Consequently, the wave function must be anti-symmetrized, which leads to the depletion of electronic charge between two hydrogen-like atoms. This depletion diminishes the screening of nuclear–nuclear electrostatic interaction, leading to repulsive forces between the two atoms. In part B, the p orbitals are included in the expansion of the one-electron wave function, which naturally leads to an anisotropic model of repulsion.
A. Isotropic classical exchange-repulsion

Consider two hydrogen-like atoms with wave functions $\phi_A$ and $\phi_B$, both with charge $Z$. If these two atoms are far apart and noninteracting, the total wave function is a (normalized) simple product,

$$\psi(r_1, r_2) = \frac{1}{\sqrt{2}} [\phi_A(r_1) \phi_B(r_2)], \quad (1)$$

and the corresponding electron density is

$$\rho(r) = 2Z \star (\psi | \psi) = Z [\phi_A^2(r) + \phi_B^2(r)]. \quad (2)$$

where electron densities are localized on atom A and atom B. (The factor of two comes from the sum of the two hydrogen electrons.)

$$\rho(r) = 2Z \star (\psi | \psi) = \frac{2Z}{2 - 2S} (\phi_A(r_1) \phi_B(r_2) - \phi_A(r_2) \phi_B(r_1))$$

$$= \frac{Z}{1 - S^2} \left[ \int \phi_A^2(r_1) \phi_B^2(r_2) dr_2 + \int \phi_A^2(r_2) \phi_B^2(r_1) dr_1 - 2 \int \phi_A(r_1) \phi_B(r_2) \phi_A(r_2) \phi_B(r_1) dr_1 \right]$$

$$= \frac{Z}{1 - S^2} \left[ \phi_A^2(r_1) + \phi_B^2(r_1) - 2S \phi_A(r_1) \phi_B(r_1) \right]. \quad (5)$$

Assuming that the overlap is small, we can expand the pre-factor using the series expansion,

$$\frac{1}{1 - S^2} \approx 1 + S^2 + S^4 + \ldots. \quad (6)$$

Taking the leading order (ignoring $S^2$ and higher order terms), the density is approximated as

$$\rho(r) = Z \star (\phi_A^2(r) + \phi_B^2(r) - 2S \phi_A(r) \phi_B(r)). \quad (7)$$

Having computed the density of the interacting hydrogen dimer, we can compute the change in density compared to the non-interacting wave function in Eq. (2),

$$\Delta \rho(r) = \rho(r) - \rho(r) = 2Z \delta \phi_A(r) \phi_B(r). \quad (8)$$

Using this change in density, we can compute the change in the electrostatic energy from the perspective of atom A,

$$\Delta E_A = Z \times \int \frac{\Delta \rho}{r_A} dr_A = 2Z^2 S^2 \int \frac{\phi_A(r_A) \phi_B(r_A)}{r_A} dr_A. \quad (9)$$

In regions of small overlap, \textit{ab initio} densities show that the product $\phi_A(r) \phi_B(r)$ is concentrated at the midpoint between atoms A and B at $r = \frac{R}{2}$. Rackers and Ponder\textsuperscript{55} show this in Fig. 3(a) using the coupled cluster single-double densities of two helium atoms. Substituting in a constant value of $r = \frac{R}{2}$, we obtain

$$\Delta E_A = \frac{4Z^2 S^2}{R} \int \phi_A(r) \phi_B(r) dr = \frac{4Z^2 S^2}{R}. \quad (10)$$

However, as the two atoms approach one another, the total wave function must be anti-symmetric and normalized,

$$\Psi(r_1, r_2) = \frac{1}{\sqrt{2 - 2S^2}} [\phi_A(r_1) \phi_B(r_2) - \phi_A(r_2) \phi_B(r_1)]. \quad (3)$$

where $S$ is the overlap integral,

$$S = \langle \phi_A | \phi_B \rangle. \quad (4)$$

In this derivation, we assume the same spin hydrogen-like wave functions because opposite spins would lead to a bonding orbital, whereas same spins would lead to repulsion.\textsuperscript{62} The electron density associated with the anti-symmetrized wave function in Eq. (3) can be computed by squaring the wave function,

$$\rho(r) = 2Z \ star (\Psi | \Psi)$$

The change in the electrostatic energy of atom B is the same as that of atom A, giving the total change in energy as

$$\Delta E = \Delta E_A + \Delta E_B = \frac{8Z^2 S^2}{R}. \quad (11)$$

As described in Chap. 6 of The Theory of Intermolecular Forces,\textsuperscript{62} this change in electrostatic energy due to the Pauli exclusion principle is precisely the exchange-repulsion energy $E_R = \Delta E$.

The derivation above is valid for two identical hydrogen-like atoms. To extend this derivation for two different atoms, we introduce the charge-like parameters $Z_A$ and $Z_B$ for atom A and B, respectively, and absorb the factor of 8 into the charge parameters. A similar extension was made in Eq. (37) of Rackers and Ponder,\textsuperscript{55} where the "size" parameters $K_A$ and $K_B$ are multiplied to $\frac{Z^2}{R}$ to give the repulsion energy. As our classical models are approximations of the true many-electron system, we choose $Z_A$ and $Z_B$ as parameters that can be fit to replicate the \textit{ab initio} SAPT2+ benchmarks. In summary, the final isotropic repulsion model for HIPPO is given by

$$E_R = Z_A S^2 R Z_B. \quad (12)$$

B. Anisotropic classical exchange-repulsion

The ground state of a hydrogen atom is the s orbital,

$$|\phi\rangle = |s\rangle = \sqrt{\frac{a^3}{\pi}} e^{-ar}. \quad (13)$$
where \( \alpha \) determines the diffusivity of the electron cloud. Isotropic repulsion is calculated by using this \( s \) orbital to compute the overlap and plugging it into Eq. (12). In this model, to make the repulsion model anisotropic, the \( p \) orbitals are included in the wave function,

\[
\langle \phi | \phi \rangle = c_1^2 + c_2^2 + c_3^2 + c_4^2 = 1,
\]

where

\[
| p_x \rangle = \sqrt{\frac{2}{\pi}} x e^{-\alpha r},
\]

and \( | p_y \rangle \) and \( | p_z \rangle \) are similarly defined.

The coefficients \( c_1, c_2, c_3, \) and \( c_4 \) must satisfy two conditions. First, they must be normalized so that

\[
\langle \phi | \phi \rangle.
\]

The dipole moment can be assigned via distributed multipole analysis (DMA), and therefore, the coefficients \( c_1, c_2, c_3, \) and \( c_4 \) can be determined. Once the coefficients are fixed, all that remains to be solved is the repulsion energy in Eq. (12). The overlap integral is

\[
S = \langle \phi | \phi \rangle = (c_1^* | s^I \rangle + c_2^* | p_x^I \rangle + c_3^* | p_y^I \rangle + c_4^* | p_z^I \rangle) \times (c_1 | s^J \rangle + c_2 | p_x^J \rangle + c_3 | p_y^J \rangle + c_4 | p_z^J \rangle).
\]

Equation (17) has a total of 16 terms; however, by taking advantage of local symmetry and using the prolate spheroidal frame, there are only six non-zero terms. The \( c_{sx}, c_{sy}, c_{sz} \) coefficients are rotated to \( c_{sx'}, c_{sy'}, c_{sz'} \), where the subscript \( I \) is used to denote the quasi-internal frame defined by the prolate spheroidal coordinates,

\[
R_I c = c_I,
\]

where \( R_I \) is a rotation matrix to the prolate spheroidal local frame. In this frame, the overlap integral is

\[
S = (c_1^* | s^I \rangle + c_2^* | p_x^I \rangle + c_3^* | p_y^I \rangle + c_4^* | p_z^I \rangle) \times (c_1 | s^J \rangle + c_2 | p_x^J \rangle + c_3 | p_y^J \rangle + c_4 | p_z^J \rangle).
\]

The \( c_i \) coefficient is isotropic and does not need to be transformed to the quasi-internal frame. The analytical forms of the six integrals, \( \langle s^I | s^J \rangle, \langle p_x^I | p_x^J \rangle, \langle p_y^I | p_y^J \rangle, \langle p_z^I | p_z^J \rangle, \langle s^I | s^J \rangle, \langle s^I | p_x^J \rangle, \langle s^I | p_y^J \rangle, \langle s^I | p_z^J \rangle, \langle p_x^I | p_x^J \rangle, \langle p_y^I | p_y^J \rangle, \langle p_z^I | p_z^J \rangle, \) are computed from Roothaan’s two-center integrals and are presented in the supplementary material. Once the overlap integral in Eq. (19) is solved, the repulsion energy is calculated by plugging in the overlap into Eq. (12). For the interested reader, the gradient and torque are derived in the supplementary material.

III. METHODS

The anisotropic repulsion model requires three parameters for each atom: the \( Z \) charge, \( \alpha \) exponent, and \( c_i \) ratio coefficient. The \( c_i \) ratio coefficient measures the relative contribution of the \( p \) orbital to the total wave function. For example, a small \( c_i \) indicates a pre-dominantly \( s \) orbital wave function. To obtain these three parameters and to validate our repulsion model, we begin our parameterization using the previously constructed S101 dimer database. This database consists of 101 unique sets of biomolecular dimers with seven different points along the dissociation curve at 0.7, 0.8, 0.9, 0.95, 1.0, 1.05, and 1.1 times the equilibrium distance. This database includes intramolecular interactions that are important in biomolecular applications and has been successfully utilized in the development of modern force fields. The details on the generation of these structures are available in the study by Wang et al. For
each geometry, we employ SAPT2+/aug-cc-pVDZ as the QM benchmark following the recommendation of Parker et al., as it strikes a good balance between computational speed and chemical accuracy. All ab initio calculations were carried out using the Psi4 software platform. For the S101 dimer database, we compare vdW2017 repulsion, isotropic repulsion, and anisotropic repulsion. The vdW2017 repulsion uses the AMOEBA standard buffered 14-7 potential, where the repulsive component was previously fit to the S101x7 database. The isotropic and anisotropic repulsion models are parameterized using the Levenberg–Marquardt least-squares algorithm. Isotropic repulsion requires Z and α, and anisotropic repulsion needs the additional cr parameter. To prevent overfitting to a short range, the dimers at 0.7, 0.8, and 0.9 times the equilibrium distance were scaled by 0.2, 0.5, and 0.8, respectively, while the remaining dimers at 0.95, 1.0, 1.05, and 1.1 times the equilibrium distance were left unchanged. The parameterization of anisotropic repulsion followed a three-step procedure. We first fit Z and α, keeping cr fixed to zero. The dipole moments were then determined using Stone’s distributed multipole analysis. The dipole moments are required in the model as the p orbital coefficients and dipole moments are related through the cr ratio coefficient. Finally, using the previously fit Z and α as the starting point, Z, α, and cr were simultaneously parameterized.

After presenting the S101 dimer database, we validate the model through examples, including water–water dimers and dimers involving halobenzenes. The purpose of the validation is twofold. First, we wanted to see whether the parameters obtained from the S101 models were parameterization transferable to molecules and dimer geometries that were not included in the test set. Second, we wanted to demonstrate the importance of anisotropic repulsion, where repulsion’s angular dependence is completely absent without the anisotropic term. Three different examples of water–water dimers are generated: water dimer dissociated along the O–O axis, water dimer rotated about its “flap-angle,” and ten stationary points and angular scans across the “flap angles,” require the anisotropic term to replicate SAPT2+ energies. Second, the “sigma-hole” phenomena of halobenzenes gives rise to a strong angular dependence on repulsion, which completely disappears when the cr ratio coefficient (which scales the p orbital contribution) is turned off. The performance of the model is benchmarked on the CPU and GPU, and we demonstrate that the novel term can be computed efficiently for a moderate-sized water box.

A. Model accuracy: Fit to the S101 dimer database

To test the accuracy and robustness of the model, we parameterized both the isotropic and anisotropic repulsion against the S101 dimer database. The repulsion parameters for isotropic and anisotropic repulsion were fit using the Levenberg–Marquardt least-squares procedure. To prevent overfitting to large magnitude short-range repulsion energies, the dimers at 0.7, 0.8, and 0.9 times the equilibrium distance were scaled by 0.2, 0.5, and 0.8, respectively. The remaining dataset of 0.95, 1.0, 1.05, and 1.1 times the equilibrium distance was unmodified. The parameters for the buffered 14-7 potential (vdW2017) were unchanged from the previous fitting of Rackers and Ponder. The optimized parameters and structures are included in the supplementary material.

The result of the parameterization is shown in Fig. 1. Figure 1(a) shows the vdW2017, isotropic, and anisotropic repulsion against SAPT2+, and Fig. 1(b) shows the same data in log scale. The root mean square errors of the three models are presented in Table I. We can immediately appreciate from Fig. 1 that the S2 models (isotropic and anisotropic) are significantly more accurate than vdW2017. In addition, on comparing the short-range root mean square error (RMSE) in Table I, we notice that the error of vdW2017 is 3–4 kcal/mol greater than the S2 models. Even at long range, the RMSE of vdW2017 is 0.83 kcal/mol, whereas the S2 models are ~0.2 kcal/mol. Here, we encounter the first limitation of the polynomial class of repulsion. The S2 models, derived from first principles, outperform vdW2017 at both short and long ranges.

The overall RMSE of vdW2017, isotropic, and anisotropic models are 2.66, 1.29, and 0.90 kcal/mol, respectively. Although the isotropic model performs reasonably well, the anisotropic model has the additional ability to reproduce SAPT to within a chemical accuracy of 1 kcal/mol. It is worth noting that the large vdW2017 error is partly mitigated by the dispersion component of the buffered 14-7 potential. Even so, the mixing of repulsion and dispersion in buffered 14-7 or Lennard–Jones 12-6 potential makes the polynomial
models less interpretable and more difficult to fit separately to energy decomposition analysis.

Next, we compare the isotropic and anisotropic repulsion. Table I highlights an improvement in the short-range category, while showing minimal change at both the intermediate and long range. This outcome demonstrates the “multipole” characteristic of electrons. When observing from a distance, the electrons appear to be spherically distributed around an atom, but at a closer distance, the anisotropy becomes apparent. By analogy to electrostatics, the monopole–monopole term decays at a slower rate \((\frac{1}{r})\) than the monopole–dipole \((\frac{1}{r^3})\) interaction. In both repulsion and electrostatics, the multipolar characteristic becomes evident as molecules approach each other. Anisotropy is necessary to capture short-range interactions.

The improvement in the overall RMSE is encouraging, especially because the S101 database consists of a diverse array of complex molecules. Even the enhanced accuracy at short range, which is 0.7 times the equilibrium distance, is noteworthy as these configurations are sporadically sampled during a room temperature molecular dynamics simulation. Here, we point out that the advantage gained from the anisotropic model is somewhat modest compared to the isotropic model (RMSE of 0.90 vs 1.29 kcal/mol, respectively). This is because the S101 database is comprised of dimers that are linearly separated along a fixed axis, i.e., the S101 database is not particularly anisotropic. In the ensuing sections, we explore dimers exhibiting greater anisotropy, where one molecule is fixed and the other is rotated. The true advantage of the anisotropic model will become apparent in the following angular survey of dimers. It will be demonstrated that in the absence of the anisotropy, the angular dependence of repulsion and the “sigma-hole” effect of halogen will be entirely neglected. Furthermore, in the rotational scans, we employ identical parameters acquired in the fitting of the S101 database. In expanding to molecules beyond the training set, we demonstrate further transferability and robustness of the model.

### B. Model validation 1: Water dimers

Water is perhaps the most important molecule in the simulation of biomolecules because many interesting biochemical reactions occur in it. Accurate modeling of water–water and water–biomolecule interaction is crucial in obtaining physically valid microscopic and macroscopic/thermodynamic results. A complete parameterization of water is beyond the scope of this paper. However, as a demonstration of the novel anisotropic repulsion model, we present three cases of the water–water dimer and show that anisotropy is critical in capturing the angular dependence of repulsion. We will explore the water–water repulsion energy along its dissociation axis, angular scan across the water “flap angle,” and look at the ten stationary points of water dimers that constitute the Smith dimers.

The global minimum structure of the water–water dimer is shown in Fig. 2. We dissociate the water–water dimer along the O–O axis and compute the repulsion energy using SAPT2+ at seven points, 0.7, 0.8, 0.9, 0.95, 1.0, 1.05, and 1.1 times the equilibrium distance. The vdW2017, isotropic, and anisotropic models are compared to the \textit{ab initio} results. All the three models do well at 0.9 times the equilibrium distance and beyond; however, the anisotropic model performs better in the short-range region. Because anisotropy is important at short range, this is an encouraging sign that the model is capturing the correct physics throughout the dissociation axis. However, both the vdW2017 and isotropic models give good results beyond the short range. This is because the monopole terms dominate at a further range. The true advantage of the anisotropic model will become evident in the “flap angle” scans and the ten Smith dimers.

Next, we explore the water potential surface along the flap angle. The flap angle shown in Fig. 3 is the rotation angle along the O–O axis of the global minimum water dimer. The energy dependence on the flap angle is well documented, and high level \textit{ab initio} calculations show that the optimized structure is at 57°.73 Rackers and Ponder showed that in the absence of anisotropic repulsion, the predicted minimum structure is at 70° due to favorable electrostatic interactions and that the true minimum of 57° is only obtained if anisotropic repulsion is considered. To test whether our new model can capture the anisotropic profile along the flap angle, we start at 0° and rotate one of the water molecules to 90°, as shown in Fig. 3. We immediately notice that the angular profile is flat from 0 to 60° in the vdW2017 and isotropic repulsion models. Only when the water molecule is sufficiently rotated, the steric clash of hydrogen causes increased repulsion. On the other hand, the anisotropic model accurately reproduces the SAPT2+ values, where the error is less than 0.25 kcal/mol along the angular scan. It should be noted that the AMOEBA water model, despite lacking anisotropic repulsion, predicts the minimum at 57°. This was obtained by special tuning of the quadrupole electrostatic moment by 73% from the DMA values.42 One advantage of the new model is that anisotropic repulsion is placed on the same level of theory as anisotropic

### Table I. S101x7 root mean square error. The S101x7 dataset was divided into short-, intermediate-, and long-range dimers. Short-range dimers are at 0.7 times the dimer equilibrium distance; intermediate-range dimers are between 0.8 and 0.95 times the equilibrium distance; and long-range dimers include datapoints at 1.0–1.1 times the equilibrium distance. The units are in kcal/mol.

<table>
<thead>
<tr>
<th></th>
<th>Total RMSE (kcal/mol)</th>
<th>Short-range RMSE (0.7) (kcal/mol)</th>
<th>Intermediate-range RMSE (0.8–0.95) (kcal/mol)</th>
<th>Long-range RMSE (1.0–1.1) (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>vdW2017 repulsion</td>
<td>2.66</td>
<td>5.94</td>
<td>2.02</td>
<td>0.83</td>
</tr>
<tr>
<td>Isotropic repulsion</td>
<td>1.29</td>
<td>3.13</td>
<td>0.76</td>
<td>0.22</td>
</tr>
<tr>
<td>Anisotropic repulsion</td>
<td>0.90</td>
<td>2.11</td>
<td>0.59</td>
<td>0.19</td>
</tr>
</tbody>
</table>
FIG. 2. Water dimer distance scan. The water dimer is scanned along the O–O axis of the minimum energy structure. At long range, all models capture repulsion energy reasonably well. However, anisotropic repulsion is most accurate at short range.

FIG. 3. Water dimer flap angle scan. The vdW2017, isotropic, and anisotropic repulsion models are compared to SAPT exchange-repulsion. The vdW2017 and isotropic models cannot capture the anisotropy across the angular scan, whereas the anisotropic model is within 0.25 kcal/mol of the SAPT reference energy.

FIG. 4. Smith water dimers. The repulsion energy relative to SAPT exchange-repulsion is computed for the ten Smith dimers using vdW2017, isotropic, and anisotropic models. The relative error is computed as (SAPT2+ repulsion) – (model repulsion). The anisotropic model has the smallest RMSE across these three models.

electrostatics. By using the anisotropic repulsion model, no additional tuning of electrostatic quadrupoles will be required.

As a final example, we investigate the Smith dimers, which are ten extensively studied stationary points of the water–water dimer. The Smith dimers provide an excellent test of the angular dependence of anisotropic repulsion as they consist of water dimers in ten different orientations. In Fig. 4, we show the Smith dimer geometries along with the repulsion energies of vdW2017, isotropic, and anisotropic models. The anisotropic model has an error of less than ∼1 kcal/mol for each dimer, and the overall RMSE is only 0.46 kcal/mol. The largest errors for the vdW2017 and isotropic model are observed for dimers 4–6, which is vastly improved using the anisotropic repulsion.

Of all the dimers in the S101 database, 33 of them involve water. The S101 dimer database was carefully constructed, including water–biomolecule dimers that are important in biomolecular applications. To demonstrate the accuracy of the water repulsion parameter, we analyzed the subset of the S101 dimer database involving water. In Table II, we appreciate the accuracy afforded by the inclusion of the anisotropic terms. Although anisotropic repulsion requires computation of additional terms, the total RMSE of the anisotropic model is only 0.58 kcal/mol, vastly outperforming the vdW2017 and isotropic repulsions.

C. Model validation 2: Halobenzene and the "sigma hole" effect

Halogenated molecules play an increasingly important role in drug discovery and development. It is estimated that 36.4% of drugs in Phase III clinical trial contain organohalogens. Successful case studies ranging from phosphodiesterase type 5 (PDE5) inhibitors to HIV-1 reverse transcriptase targets involving halogenated compounds have been reported. Accurate representation of protein–ligand complexes involving halogenated molecules is important from both the theoretical and practical perspectives.

One phenomenon exhibited by halogenated molecules is the so-called "σ-hole" (sigma-hole) effect, where a partial positive charge is found at the tip of a halogen that is bonded to an electronegative unit. This partial positive charge interacts favorably with a partial negatively charged atom and forms a linear bond. It is interesting that although the overall attractiveness is driven by electrostatics, the linearity of the halogen bonds is driven by repulsion. By systematically varying the halogen bond tilt angle and using energy decomposition analysis, Stone showed that the linearity of the halogen bond is primarily driven by repulsion, where a deviation from the linearity resulted in increased repulsion. We set out to test whether our anisotropic model can capture this phenomenon. Following the examples from Rackers and Ponder, we investigate the σ-hole effect of water–chlorobenzene, acetone–bromobenzene, and peptide–chlorobenzene dimers.

The water–chlorobenzene dimer, as suggested by Hage et al., was selected as a test to determine whether our anisotropic repulsion model can capture the angular dependence of the halogen bond. The water–chlorobenzene dimer was minimized at the MP2/aug-cc-pVTZ level of theory, and the halogen bond angle was varied from 0 to 80°. In Fig. 5, we show the change in repulsion as a function of the O–Cl halogen bond angle. We immediately notice that vdW2017
TABLE II. Water in S101x7 RMSE. The subset of the S101x7 dataset involving water was divided into short-, intermediate-, and long-range dimers. Short-range dimers are at 0.7 times the dimer equilibrium distance; intermediate-range dimers are between 0.8 and 0.95 times the equilibrium distance; and long-range dimers include datapoints at 1.0–1.1 times the equilibrium distance. The units are in kcal/mol.

<table>
<thead>
<tr>
<th></th>
<th>Total RMSE (kcal/mol)</th>
<th>Short-range RMSE (0.7) (kcal/mol)</th>
<th>Intermediate-range RMSE (0.8–0.95) (kcal/mol)</th>
<th>Long-range RMSE (1.0–1.1) (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>vdW2017 repulsion</td>
<td>2.24</td>
<td>4.68</td>
<td>1.86</td>
<td>0.79</td>
</tr>
<tr>
<td>Isotropic repulsion</td>
<td>1.21</td>
<td>3.01</td>
<td>0.57</td>
<td>0.19</td>
</tr>
<tr>
<td>Anisotropic repulsion</td>
<td>0.58</td>
<td>1.37</td>
<td>0.35</td>
<td>0.14</td>
</tr>
</tbody>
</table>

and isotropic repulsion are flat along the angular scan and only increase near 80°, where the hydrogen atom of benzene and oxygen atom of water clash. On the other hand, the anisotropic model replicates the \textit{ab initio} repulsion values to within 0.25 kcal/mol along the angular scan.

To demonstrate that the angular dependence on energy is not obtained from a fortuitous parameterization procedure, we use the same \( Z \) and \( \alpha \) parameters from the anisotropic model but set the chlorine \( c_r = 0 \), effectively turning off the \( p \) orbital terms. This is equivalent to the \textit{isotropic} model; however, \( Z \) and \( \alpha \) are obtained...
from the parameterization of the anisotropic model. In Fig. 5(b), when the $c_r$ term is turned off, we reproduce a repulsion profile that is similar to that of vdW2017 and isotropic repulsion of Fig. 5(a), showing that the $p$ orbital terms mediate anisotropic repulsion.

We follow a similar procedure using the acetone–bromobenzene and N-methylacetamide (NMA)–chlorobenzene dimers. The acetone–bromobenzene dimer was proposed by Riley et al. as a probe to assess halogen bonding with a carbonyl group. The NMA–chlorobenzene dimer was studied by Adasme-Carreno et al. as a proxy to investigate the halogen bonding between peptide and drug-like molecules, as NMA forms the peptide backbone. Similar to the previous water–chlorobenzene dimer example, the two dimer systems were minimized at the MP2/aug-cc-pVTZ level and rotated about the O–halogen bonds, as shown in Figs. 6 and 7. We observe the same trend as above, where the vdW2017 and isotropic repulsion models do not capture anisotropy until there is significant overlap of atoms. Using the same $Z$ and $\alpha$ parameters, we again set the halogen (chlorine and bromine) $c_r = 0$ and show that without the $p$ orbital, the effect of anisotropy is considerably diminished. Through three examples of halogen bonding, we demonstrate that the $c_r$ parameter drives the angular profile of repulsion and enforces linearity along the halogen bond.

D. Speed and validation

Capturing interesting biomolecular phenomena requires long timescales ranging from nanosecond to milliseconds. Therefore, computational efficiency is one of the major bottlenecks in force field development. Fortunately, the new repulsion term is pairwise and can be truncated at short range (\(\sim 6\, \text{Å}\)), which allows faster computation of energy and gradient. We implemented our model in Tinker (CPU) and Tinker (GPU). As a benchmark, a moderate-sized water box was simulated using the AMOEBA, HIPPO, and HIPPO + new model, using the standard protocol described in the methods section. The HIPPO + new model uses all the HIPPO potential functions except HIPPO repulsion, which is replaced with the new repulsion. A CPU simulation of a \(30 \times 30 \times 30\, \text{Å}^3\) water box (900 water molecules) was run for 5000 MD steps (i.e., 5000 energy and gradient evaluations). The AMOEBA, HIPPO, and HIPPO + new model took 588, 656, and 859 s respectively. Although the HIPPO + new model involves more calculation, this cost is offset by the accuracy it provides, as demonstrated above. The same water box was used to benchmark the GPU implementation of the new model. As presented in Table III, the performance of the HIPPO + new model is comparable to HIPPO, both of which are ever so slightly slower than AMOEBA. Similar to the CPU implementation, the additional accuracy of anisotropic repulsion is paid for in computational cost.

V. DISCUSSION AND CONCLUSIONS

We have developed a new repulsion model that extends Salem’s isotropic model to include anisotropy through the inclusion of $p$ orbitals. By the addition of only one more parameter for anisotropy, we achieve an rms error of 0.9 kcal/mol on our extensive S101 dimer dataset, reproduce accurate water–water angular...
repulsion energies, and capture the d-hole effect of halobenzene systems. We argue that anisotropic repulsion must be considered if anisotropy is also present in the electrostatics model. From a theoretical perspective, this is desirable because repulsion and electrostatics occupy equivalent levels in the perturbation theory. From a practical perspective, special tuning of electrostatic moments (such as the AMOEBA water discussed above) must be considered if one chooses to use anisotropic electrostatics with isotropic repulsion. Here, by developing an anisotropic repulsion model, we place repulsion on the same level of theory as anisotropic electrostatics.

We must acknowledge the long history in the development of anisotropic repulsion potentials. This model is certainly not the first to do so. However, there are a couple of noteworthy features that make this model stand out. First, we include anisotropy from an intuitive, first-principles approach. Salem used the s orbital to compute the overlap for the original $\frac{d}{cr}$ model. We simply extended this model by constructing a linear combination of s and p orbitals. Second, we connect the orbital picture with the physically observable dipole moments, which are directly computed from the DMA procedure. Third, the simple pairwise interactions allow for truncation at a short range, making this function scalable to larger systems.

One question that remains is whether this model can be further extended to include the d orbitals. In this work, the d orbitals were not included for computational efficiency. The linear combination of s orbitals and p orbitals (p, p, p) constitutes a wave function with 4 (1 + 3) terms [Eq. (14)], and the overlap integral includes the product of two wave functions, requiring computation of $4 \times 4 = 16$ terms. However, by taking advantage of the local symmetry of the overlap integral, we can reduce to six terms, as shown in Eq. (19). The d orbitals in spherical basis has five terms, and therefore, the wave function of s, p, and d orbitals will be a linear combination of $9 (1 + 3 + 5)$ terms. The overlap would naively have $9 \times 9 = 81$ terms, which can be further reduced by exploiting the local symmetry of the overlap integrals. As shown in this paper, just by including p orbitals, we can fit the S101 database within the chemical accuracy and capture many interesting anisotropic phenomena. We would be curious to see where this model is insufficient and requires the inclusion of d orbitals. Incorporating the d orbitals will be reasonably straightforward by following Sec. III and the supplementary material.

Another consideration of the current model is that although only p orbitals are included, it does not neglect the quadrupole moments. It can be shown that the (traceless) quadrupole moment,

$$\Theta_{ij} = \langle \phi | \frac{1}{2} 3r_i r_j - r_i^2 \delta_{ij} | \phi \rangle$$

is non-zero using the wave function defined in Eq. (14). Although the dipole moments were used to fit the C_r parameter in this work, future developments of the model could include information from the quadrupole moments, as well as include d orbitals in the wave function.

A final consideration is the automated generation of parameters.86–90 Automated parameter generators have been successfully utilized in the recent statistical assessment of modeling proteins and ligands binding free energy challenges91,92 and in lead optimization and development.93,94 For this purpose, we suggest that the C_r parameter is set to zero unless sufficient angular scans are provided in the fitting procedure. The parameterization of C_r may require fine tuning against the ab initio EDA results across angular scans of the molecule. Although angular scans can be included in the automation procedure, a simpler protocol would be to use pre-determined “atom-class” parameters, utilizing the isotropic model. This would effectively result in a hybrid isotropic–anisotropic model, where extensively parameterized molecules, such as water, would have an anisotropic potential, whereas the small molecule of interest with less data would use a class-based isotropic potential. There are two justifications for this procedure: first, the isotropic model alone performs decently well, with an RMSE of only 1.29 kcal/mol for the S101 database. Although the anisotropic model is more accurate when angular data are scarce, the isotropic approximation generates reasonable results. Second, even in the parameterization of the S101 dimer database, there are atoms where the C_r parameter is set to 0. Some molecules did not have sufficient angular scans to determine the C_r parameter, so isotropic parameters were used instead. As presented in Table I, we still obtain a very small RMSE for this hybrid isotropic–anisotropic model.

The derivation and result of the new model highlight the importance of anisotropic repulsion in the context of biomolecular simulations. The theory and framework of this model is applicable to any force field, although we have implemented our model in the context of the HIPPO force field. Our parameterization of the S101 dimer database provides a good starting point for force field development, and we plan to further develop this model to be used in the simulation of general biomolecular systems.

**SUPPLEMENTARY MATERIAL**

The supplementary material contains additional derivations, including wave function coefficients from dipole moment, overlap integrals, the repulsion gradient and torque, and definitions of rotation matrices used. An archive file with coordinates and the SAPT integrals used. A file with the parameterization of the S101 dimer database provides a good starting point for force field development, and we plan to further develop this model to be used in the simulation of general biomolecular systems.

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**AUTHOR DECLARATIONS**

**Conflict of Interest**

J.W.P. is a co-founder and member of the Board of Directors of Qubit Pharmaceuticals.

**Author Contributions**

Moses K. J. Chung: Conceptualization (equal); Investigation (equal); Methodology (equal); Software (equal); Writing – original draft (equal); Writing – review & editing (equal). Jay W. Ponder: Conceptualization (equal); Funding acquisition (equal); Investigation (equal); Methodology (equal); Software (equal); Writing – original draft (equal); Writing – review & editing (equal).
REFERENCES


Supplementary Material

Classical Exchange Repulsion: An Anisotropic Repulsion Model

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I. Determining wavefunction coefficients from the dipole moment

First, we show that the ratio of the $p$ orbital coefficients $c_x$, $c_y$, $c_z$ are proportional to the dipole moments. In the main text, we expanded the hydrogen-like one-electron wavefunction as

$$ |\phi\rangle = c_s|s\rangle + c_x|p_x\rangle + c_y|p_y\rangle + c_z|p_z\rangle, $$

where

$$ |s\rangle = \sqrt{\frac{\alpha^3}{\pi}} e^{-\alpha r}, $$

$$ |p_x\rangle = \sqrt{\frac{\alpha^5}{\pi}} x e^{-\alpha r}, $$

and similarly defined for $|p_y\rangle$ and $|p_z\rangle$.

The $p_x$ dipole moment of this atom is

$$ p_x = \langle \phi | x | \phi \rangle $$

$$ = (c_s\langle s | + c_x\langle p_x | + c_y\langle p_y | + c_z\langle p_z |) x (c_s|s\rangle + c_x|p_x\rangle + c_y|p_y\rangle + c_z|p_z\rangle) $$

$$ = c_s c_x \langle s | p_x \rangle + c_x c_s \langle p_x | s \rangle = 2 c_s c_x \langle s | p_x \rangle. $$

Likewise, the $p_y$ and $p_z$ dipole moments are

$$ p_y = 2 c_s c_y \langle s | p_y \rangle, $$

$$ p_z = 2 c_s c_z \langle s | p_z \rangle. $$

The integrals $\langle s | p_x \rangle = \langle s | p_y \rangle = \langle s | p_z \rangle$ are all equal, which is apparent by using Eq. (2) and integrating over space. Therefore, the ratios $p_x : p_y : p_z$ is equal to the ratio of the coefficients, $c_x : c_y : c_z$. In other words, the observable dipole moment can be connected to the coefficients.
The three dipole moments $p_x, p_y, p_z$ yield two ratios (for example, given $p_x : p_y$ and $p_x : p_z$, the ratio $p_y : p_z$ is fixed). There are four variables $c_s, c_x, c_y, c_z$ to solve for, two ratios of dipole moments, and one normalizing condition

$$\langle \phi | \phi \rangle = c_s^2 + c_x^2 + c_y^2 + c_z^2 = 1. \quad (5)$$

Thus, there is only one free degree of freedom. We call this degree of freedom $c_r$ and define it as

$$c_r = \frac{c_s^2 + c_y^2 + c_z^2}{c_x^2}. \quad (6)$$

The only parameter to be fit to SAPT reference data is $c_r$. Given this value and the dipole moments $p_x, p_y, p_z$ from distributed multipole analysis, the four coefficients $c_s, c_x, c_y, c_z$ can be solved.

The coefficient $c_s$ is solved by

$$1 + c_r = 1 + \frac{c_s^2 + c_y^2 + c_z^2}{c_x^2} = \frac{1}{c_x^2} \Rightarrow c_s = \frac{1}{\sqrt{1 + c_r}}. \quad (7)$$

The coefficient $c_x$ is solved by

$$c_s^2 = c_x^2 + c_y^2 + c_z^2 = c_r c_s^2$$

$$= c_x^2 \left( 1 + \left( \frac{c_y}{c_x} \right)^2 + \left( \frac{c_z}{c_x} \right)^2 \right) = c_x^2 \left( 1 + \left( \frac{p_y}{p_x} \right)^2 + \left( \frac{p_z}{p_x} \right)^2 \right) = c_r c_x^2. \quad (8)$$

And since the ratio of the dipole moments are known, $c_s$ can be computed. The $c_y$ and $c_z$ coefficients can also be solved from the ratios of dipole moments

$$c_y = \frac{p_y}{p_x}, \quad c_z = \frac{p_z}{p_x}. \quad (9)$$
II. Integrals for the overlap

In this section, the overlap integrals \( \langle s^A \mid s^B \rangle, \langle p_x^A \mid p_x^B \rangle, \langle p_y^A \mid p_y^B \rangle, \langle p_z^A \mid p_z^B \rangle, \langle s^A \mid p_x^B \rangle, \langle p_x^A \mid s^B \rangle \) are displayed. As a model choice, we let the \( s \) and \( p \) orbitals have the same exponent coefficient, \( \alpha = \alpha_s = \alpha_p \) in Eq. (2). The overlap integrals were solved by Roothaan using the prolate spheroidal coordinates. Analytic solutions exist for the two cases \( \alpha_A = \alpha_B \) and \( \alpha_A \neq \alpha_B \). The intermolecular distance in the quasi-internal (prolate spheroidal) frame is \( z_I \).

Case 1: \( \alpha_A = \alpha_B \)

\[
\langle s^A \mid s^B \rangle = \left(1 + \alpha z_I + \frac{1}{3} (\alpha z_I)^2\right) e^{-\alpha z_I},
\]
\[
\langle p_x^A \mid p_x^B \rangle = \left(1 + \alpha z_I + \frac{2}{5} (\alpha z_I)^2 + \frac{1}{15} (\alpha z_I)^3\right) e^{-\alpha z_I},
\]
\[
\langle p_z^A \mid p_z^B \rangle = \left(1 + \alpha z_I + \frac{1}{5} (\alpha z_I)^2 - \frac{2}{15} (\alpha z_I)^3 - \frac{1}{15} (\alpha z_I)^4\right) e^{-\alpha z_I},
\]
\[
\langle s^A \mid p_x^B \rangle = -\alpha z_I \left(1 + \alpha z_I + \frac{1}{3} (\alpha z_I)^2\right) e^{-\alpha z_I},
\]
\[
\langle p_z^A \mid s^B \rangle = -\langle s^A \mid p_z^B \rangle,
\]
\[
\langle p_x^A \mid p_x^B \rangle = \langle p_x^A \mid p_x^B \rangle,
\]

Case 2: \( \alpha_A \neq \alpha_B \)

We first define some intermediate terms:
\[ \alpha = \frac{1}{2} (\alpha_A + \alpha_B), \]
\[ \tau = \frac{\alpha_A - \alpha_B}{\alpha_A + \alpha_B}, \]
\[ \rho = \alpha z, \]
\[ \rho_A = \alpha_A z, \]
\[ \rho_B = \alpha_B z, \]
\[ \kappa = \frac{\alpha_A^2 + \alpha_B^2}{\alpha_A^2 - \alpha_B^2} \]

After having defined these intermediate terms, the overlap integrals are

\[ \langle s^A | s^B \rangle = \frac{\sqrt{1 - \tau^2}}{\tau \rho} \left( -(1 - \kappa)(2(1 + \kappa) + \rho_A)e^{-\rho_A} + (1 + \kappa)(2(1 - \kappa) + \rho_B)e^{-\rho_B} \right), \]  
(16)

\[ \langle p_2^A | p_2^B \rangle = \frac{1}{\tau \rho^3 \sqrt{1 - \tau^2}} \left( -(1 - \kappa)^2(24(1 + \kappa)^2(1 + \rho_A) + 12(1 + \kappa)\rho_A^2 + 2\rho^3_A)e^{-\rho_A} \right. \]
\[ \left. + (1 + \kappa)^2(24(1 - \kappa)^2(1 + \rho_B) + 12(1 - \kappa)\rho_B^2 + 2\rho^3_B)e^{-\rho_B} \right), \]  
(17)

\[ \langle p_2^A | p_2^B \rangle = \frac{-1}{\tau \rho^3 \sqrt{1 - \tau^2}} \left( -(1 - \kappa)^2 \left( 48(1 + \kappa)^2 \left( 1 + \rho_A + \frac{1}{2} \rho_A^2 \right) + 2(5 + 6\kappa)\rho_A^3 + 2\rho_A^4 \right) e^{-\rho_A} \right. \]
\[ \left. + (1 + \kappa)^2 \left( 48(1 - \kappa)^2 \left( 1 + \rho_A + \frac{1}{2} \rho_B^2 \right) + 2(5 - 6\kappa)\rho_B^3 + 2\rho_B^4 \right) e^{-\rho_B} \right), \]  
(18)

\[ \langle s^A | p_2^B \rangle = \frac{\sqrt{1 - \tau}}{\tau \rho_2^2 (1 - \tau)} \left( -(1 - \kappa)(6(1 + \kappa)(1 + \rho_A) + 2\rho^3_A)e^{-\rho_A} \right. \]
\[ \left. + (1 + \kappa)(6(1 - \kappa)(1 + \rho_B) + 4(1 - \kappa)\rho_B^3 + \rho_B^3)e^{-\rho_B} \right), \]  
(19)

\[ \langle p_2^A | s^B \rangle = \frac{\sqrt{1 - \tau}}{\tau \rho^2 (1 - \tau)} \left( -(1 - \kappa)(6(1 + \kappa)^2(1 + \rho_A) + 4(1 + \kappa)\rho_A^2 + \rho_A^3)e^{-\rho_A} \right. \]
\[ \left. + (1 + \kappa)^2(6(1 - \kappa)(1 + \rho_B) + 2\rho_B^3)e^{-\rho_B} \right), \]  
(20)

\[ \langle p_2^A | p_2^B \rangle = \langle p_2^A | p_2^B \rangle, \]  
(21)
III. Repulsion Gradient

In the main text, the repulsion energy $E_R$ between atoms $A$ and $B$ is

$$E_R = Z_A Z_B \frac{S^2}{R},$$

(23)

where $Z_A$ and $Z_B$ is the empirical charge on atoms $A$ and $B$, respectively, $R$ is the intermolecular distance, and $S$ is the overlap integral

$$S = c_x^A c_x^B \langle s^A | s^B \rangle + c_x^A c_y^B \langle p_x^A | p_x^B \rangle + c_y^A c_y^B \langle p_y^A | p_y^B \rangle + c_z^A c_z^B \langle p_z^A | p_z^B \rangle$$

(24)

$$+ c_x^A c_z^B \langle s^A | p_x^B \rangle + c_z^A c_x^B \langle p_z^A | s^B \rangle.$$ 

The subscript $I$ denotes that the coefficients are rotated into the quasi-internal (prolate spheroidal) frame so that many overlap terms would cancel. Taking the gradient of repulsion along the $i = x, y, z$ component,

$$\nabla_i (E_R) = Z_A Z_B \left[ \nabla_i \left( \frac{1}{R} \right) S^2 + \frac{2S}{R} \nabla_i (S) \right].$$

(25)

The gradient of the first term is simple

$$\nabla_i \left( \frac{1}{R} \right) = -\frac{R_i}{R^3}.$$ 

(26)

The gradient of the second term requires more work because the coefficients $c_{xI}, c_{yI}, c_{zI}$ depend on the quasi-internal reference frame.

$$\nabla_i (S) =$$

$$c_x^A c_x^B \nabla_i \langle s^A | s^B \rangle + c_x^A c_y^B \nabla_i \langle p_x^A | p_x^B \rangle + c_y^A c_y^B \nabla_i \langle p_y^A | p_y^B \rangle + c_z^A c_z^B \nabla_i \langle p_z^A | p_z^B \rangle$$

$$+ c_x^A c_z^B \nabla_i \langle s^A | p_x^B \rangle + c_z^A c_x^B \nabla_i \langle p_z^A | s^B \rangle$$

$$+ \nabla_i \left( c_x^A c_x^B \langle p_x^A | p_x^B \rangle \right) + \nabla_i \left( c_y^A c_y^B \langle p_y^A | p_y^B \rangle \right) + \nabla_i \left( c_z^A c_z^B \langle p_z^A | p_z^B \rangle \right) + \nabla_i \left( c_x^A c_z^B \langle p_z^A | p_x^B \rangle \right)$$

$$+ c_x^A \nabla_i \left( c_x^B \langle p_x^A | p_x^B \rangle \right) + c_y^A \nabla_i \left( c_y^B \langle p_y^A | p_y^B \rangle \right) + c_z^A \nabla_i \left( c_z^B \langle p_z^A | p_z^B \rangle \right) + c_x^A \nabla_i \left( c_z^B \langle p_z^A | s^B \rangle \right).$$

(27)
The first term is

\[ \nabla_i (s^A|s^B) = \frac{\partial}{\partial r_i} (s^A|s^B) \]

\[ = \frac{\partial x_i}{\partial r_i} \frac{\partial}{\partial x_i} (s^A|s^B) + \frac{\partial y_i}{\partial r_i} \frac{\partial}{\partial y_i} (s^A|s^B) + \frac{\partial z_i}{\partial r_i} \frac{\partial}{\partial z_i} (s^A|s^B) \]

\[ = \frac{\partial z_i}{\partial r_i} \frac{\partial}{\partial z_i} (s^A|s^B), \tag{28} \]

since \((s^A|s^B)\) (Eq. (10) and Eq. (17)) only depend on \(z_i\). Similarly, gradients of the remaining 5 integrals also only depend on \(z_i\). The \(\frac{\partial z_i}{\partial r_i}\) pre-factor are elements from the rotation operator that is applied to global coefficients to obtain quasi-internal frame coefficients. As in the previous section, we express the overlap integral gradient for two cases where \(\alpha_A = \alpha_B\) and \(\alpha_A \neq \alpha_B\).

These gradients are taken directly by differentiating Eq. (10) - (22).

**Case 1: \(\alpha_A = \alpha_B\)**

\[ \frac{\partial}{\partial z_i} (s^A|s^B) = - \frac{1}{3} \alpha^2 z_i (1 + \alpha z_i) e^{-\alpha z_i}, \tag{29} \]

\[ \frac{\partial}{\partial z_i} (p_x^A|p_x^B) = - \frac{1}{5} \alpha^2 z_i \left(1 + \alpha z_i + \frac{1}{3} (\alpha z_i)^2\right) e^{-\alpha z_i}, \tag{30} \]

\[ \frac{\partial}{\partial z_i} (p_y^A|p_y^B) = - \frac{3}{5} \alpha^2 z_i \left(1 + \alpha z_i + \frac{2}{9} (\alpha z_i)^2 - \frac{1}{9} (\alpha z_i)^3\right) e^{-\alpha z_i}, \tag{31} \]

\[ \frac{\partial}{\partial z_i} (s^A|p_y^B) = - \frac{1}{2} \alpha \left(1 + \alpha z_i - \frac{1}{3} (\alpha z_i)^3\right) e^{-\alpha z_i}, \tag{32} \]

\[ \frac{\partial}{\partial z_i} (p_x^A|s^B) = - \frac{\partial}{\partial z_i} (s^A|p_x^B), \tag{33} \]

\[ \frac{\partial}{\partial z_i} (p_y^A|p_y^B) = \frac{\partial}{\partial z_i} (p_x^A|p_x^B). \tag{34} \]

**Case 2: \(\alpha_A \neq \alpha_B\)**
\[
\frac{\partial}{\partial z_l} \langle s^A | s^B \rangle = \frac{\sqrt{1 - \tau^2}}{z_l \tau \rho^2} \left[ (1 - \kappa)(2 + \kappa)(1 + \rho_A) + \rho_A^2 \right] e^{-\rho_A}
\]

\[
- (1 + \kappa)(2 - \kappa)(1 + \rho_B) + \rho_B^2 \right] e^{-\rho_B},
\]

\[
\frac{\partial}{\partial z_l} \langle p_x^A | p_x^B \rangle = \frac{1}{z_l \tau \rho^2 \sqrt{1 - \tau^2}} \left[ (2 - \kappa)^2(36 + \kappa)^2(1 + \rho_A) + 6(1 + \kappa)(1 + 2(1 + \kappa)) \rho_A^2 
\]

\[
+ 6(1 + \kappa) \rho_A^2 + \rho_A^4 \right] e^{-\rho_A}
\]

\[
- 2(1 + \kappa)^2(36(1 - \kappa)^2(1 + \rho_B) + 6(1 - \kappa)(1 + 2(1 - \kappa)) \rho_B^2 
\]

\[
+ 6(1 - \kappa) \rho_B^2 + \rho_B^4 \right] e^{-\rho_B},
\]

\[
\frac{\partial}{\partial z_l} \langle p_y^A | p_y^B \rangle = \frac{-2}{z_l \tau \rho^2 \sqrt{1 - \tau^2}} \left[ (1 - \kappa)^2 \left( 72(1 + \kappa)^2(1 + \rho_A) + \frac{1}{2} \rho_A^2 + \frac{1}{6} \rho_A^3 \right) + 2(2 + 3\kappa) \rho_A^4 
\]

\[
+ \rho_A^5 \right] e^{-\rho_A}
\]

\[
- (1 + \kappa)^2 \left( 72(1 - \kappa)^2(1 + \rho_B) + \frac{1}{2} \rho_B^2 + \frac{1}{6} \rho_B^3 \right) + 2(2 - 3\kappa) \rho_B^4 
\]

\[
+ \rho_B^5 \right] e^{-\rho_B},
\]

\[
\frac{\partial}{\partial z_l} \langle s^A | p_x^B \rangle = \frac{-\sqrt{1 + \tau}}{z_l \tau \rho^2(1 - \tau)} \left[ 2(1 - \kappa)^2 \left( (1 + \rho_A) + \frac{1}{2} \rho_A^2 \right) + \rho_A^3 \right] e^{-\rho_A}
\]

\[
+ (1 + \kappa) \left[ -12(1 - \kappa)^2(1 + \rho_B) + \frac{1}{2} \rho_B^2 \right] + (1 - 4(1 - \kappa)) \rho_B^3 - \rho_B^4 \right] e^{-\rho_B},
\]

\[
\frac{\partial}{\partial z_l} \langle p_y^A | s^B \rangle = \frac{-\sqrt{1 - \tau}}{z_l \tau \rho^2(1 + \tau)} \left[ (1 - \kappa) \left( -12(1 + \kappa)^2 \left( (1 + \rho_A) + \frac{1}{2} \rho_A^2 \right) + (1 - 4(1 + \kappa)) \rho_A^3 
\right.
\]

\[
- \rho_A^4 \right] e^{-\rho_A} + 2(1 + \kappa)^2 \left( 6(1 - \kappa)^2(1 + \rho_B) + \frac{1}{2} \rho_B^2 \right) + \rho_B^3 \right] e^{-\rho_B},
\]

\[
\frac{\partial}{\partial z_l} \langle p_x^A | p_y^B \rangle = \langle p_x^A | p_y^B \rangle.
\]

Having solved the derivative of overlap integrals, the first six terms in Eq. (27) can be solved.

The remaining terms involve derivatives such as \( \nabla_i(c_{x_i}) \), which can be expanded as

\[
\nabla_i(c_{x_i}) = \frac{\partial}{\partial r_i} \langle c_{x_i} \rangle = \frac{\partial x_i}{\partial r_i} \frac{\partial}{\partial x_i} \langle c_{x_i} \rangle + \frac{\partial y_i}{\partial r_i} \frac{\partial}{\partial y_i} \langle c_{x_i} \rangle + \frac{\partial z_i}{\partial r_i} \frac{\partial}{\partial z_i} \langle c_{x_i} \rangle.
\]
\( \frac{\partial x_i}{\partial r_i}, \frac{\partial y_i}{\partial r_i}, \frac{\partial z_i}{\partial r_i} \) are elements of the rotation matrix that transform global coefficients to quasi-internal local coefficients. Next, we must solve how the quasi-internal coefficients change with respect to quasi-internal coordinates, i.e., the terms \( \frac{\partial}{\partial x_i} (c_{x_i}), \frac{\partial}{\partial y_i} (c_{x_i}), \frac{\partial}{\partial z_i} (c_{x_i}) \). More generally, let’s solve how the quasi-internal coefficient vector changes with respect to the coordinates \( \frac{\partial}{\partial x_i} (c_i), \frac{\partial}{\partial y_i} (c_i), \frac{\partial}{\partial z_i} (c_i) \).

We first solve for \( \frac{\partial}{\partial x_i} (c_i) \). In the quasi-internal frame, a small change in \( d_{x_i} \) direction is equivalent to applying a small rotation matrix in the y-direction \( R_y(-d\theta) \):

\[
R_y(-d\theta) = \begin{bmatrix}
\cos(-d\theta) & 0 & \sin(-d\theta) \\
0 & 1 & 0 \\
-\sin(-d\theta) & 0 & \cos(-d\theta)
\end{bmatrix} = \begin{bmatrix}
\cos(d\theta) & 0 & -\sin(d\theta) \\
0 & 1 & 0 \\
\sin(d\theta) & 0 & \cos(d\theta)
\end{bmatrix}.
\]

In the limit of small angles,

\[
R_y(-d\theta) = \begin{bmatrix}
1 & 0 & -d\theta \\
0 & 1 & 0 \\
d\theta & 0 & 1
\end{bmatrix} = \begin{bmatrix}
1 & 0 & -dx \\
0 & 1 & 0 \\
dx/r & 0 & 1
\end{bmatrix} = R_y(dx_i),
\]

where \( r \) is the interatomic distance. Taking the derivative,

\[
\frac{\partial}{\partial x_i} (c_i) = \lim_{dx_i \to 0} \frac{R_y(dx_i) c_i - R_y(-dx_i) c_i}{2dx_i} = \begin{bmatrix}
-c_{x_i} \\
r \\
0
\end{bmatrix}.
\]

Next, we solve for \( \frac{\partial}{\partial y_i} (c_i) \). In the quasi-internal frame, a small change in \( d_{y_i} \) direction is equivalent to applying a small rotation matrix in the x-direction \( R_x(d\theta) \):

\[
R_x(d\theta) = \begin{bmatrix}
1 & 0 & 0 \\
0 & \cos(d\theta) & -\sin(d\theta) \\
0 & \sin(d\theta) & \cos(d\theta)
\end{bmatrix}.
\]

In the limit of small angles,
\begin{equation}
R_x(d\theta) = \begin{bmatrix}
1 & 0 & 0 \\
0 & 1 & -d\theta \\
0 & d\theta & 1 \\
\end{bmatrix} = \begin{bmatrix}
1 & 0 & 0 \\
0 & 1 & -\frac{dy}{r} \\
0 & \frac{dy}{r} & 1 \\
\end{bmatrix} = R_x(dy).
\end{equation}

Taking the derivative,
\begin{equation}
\frac{\partial}{\partial y_l} (c_l) = \lim_{dy_l \to 0} \frac{R_x(dy_l)c_l - R_x(-dy_l)c_l}{2dy_l} = \begin{bmatrix}
0 \\
-\frac{c_{zl}}{r} \\
\frac{c_{yl}}{r} \\
\end{bmatrix}.
\end{equation}

Finally, \( \frac{\partial}{\partial z_l} (c_l) = 0 \) since moving in the \( z_l \) direction does not change the quasi-internal coefficients. The derivatives of the coefficients can be summarized as follows:
\begin{equation}
\nabla_l (c_l) = \frac{\partial}{\partial r_l} (c_l) = \begin{bmatrix}
-\frac{c_{zl}}{r} \\
\frac{c_{xl}}{r} \\
\frac{c_{yl}}{r} \\
\end{bmatrix} + \begin{bmatrix}
0 \\
0 \\
-\frac{c_{zl}}{r} \\
\end{bmatrix}.
\end{equation}

Having solved the derivatives of the coefficient, Eq. (27) can be evaluated.
IV. Repulsion Torque

The torque on each atom can be transformed into a force on adjacent atoms as described by Segui, Pedersen, and Darden. Torque is defined as the derivative with respect to small changes in angle. The torque of the repulsion function is

$$\frac{\partial}{\partial \theta_i} (E_R) = Z_A Z_B \left[ \frac{\partial}{\partial \theta_i} \left( \frac{S^2}{R} \right) \right] = Z_A Z_B \frac{2S}{R} \frac{\partial}{\partial \theta_i} (S). \quad (49)$$

The angular derivative only changes the $c_x$, $c_y$, $c_z$ coefficients of Eq. (1). Starting from coefficients in the global frame, applying an infinitesimal rotation $\frac{\partial}{\partial \theta_i}$ would result in the following transformations:

$$\frac{\partial}{\partial \theta_x} \begin{bmatrix} c_{xG} \\ c_{yG} \\ c_{zG} \end{bmatrix} = \begin{bmatrix} 0 & 0 & 0 \\ 0 & 0 & -1 \\ 0 & 1 & 0 \end{bmatrix} \begin{bmatrix} c_{xG} \\ c_{yG} \\ c_{zG} \end{bmatrix} = \begin{bmatrix} 0 \\ -c_{zG} \\ c_{yG} \end{bmatrix}, \quad (50)$$

$$\frac{\partial}{\partial \theta_y} \begin{bmatrix} c_{xG} \\ c_{yG} \\ c_{zG} \end{bmatrix} = \begin{bmatrix} 0 & 0 & 1 \\ 0 & 0 & 0 \\ -1 & 0 & 0 \end{bmatrix} \begin{bmatrix} c_{xG} \\ c_{yG} \\ c_{zG} \end{bmatrix} = \begin{bmatrix} c_{zG} \\ 0 \\ -c_{xG} \end{bmatrix}, \quad (51)$$

$$\frac{\partial}{\partial \theta_z} \begin{bmatrix} c_{xG} \\ c_{yG} \\ c_{zG} \end{bmatrix} = \begin{bmatrix} 0 & -1 & 0 \\ 1 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix} \begin{bmatrix} c_{xG} \\ c_{yG} \\ c_{zG} \end{bmatrix} = \begin{bmatrix} -c_{yG} \\ c_{xG} \\ 0 \end{bmatrix}. \quad (52)$$

After applying these transformations, the torque is computed by Eq. (49). As an example, the torque of atom $B$ in the $x$ direction will be computed. From Eq. (50), the global coefficients of atom $B$ change to

$$\begin{bmatrix} c^B_{xG} \\ c^B_{yG} \\ c^B_{zG} \end{bmatrix} \rightarrow \begin{bmatrix} 0 \\ -c^B_{zG} \\ c^B_{yG} \end{bmatrix} = \tau_x \left( \mathbf{e}^B_G \right), \quad (53)$$

where $\tau_x$ denotes that we are interest in the torque in the $x$ direction. $\tau_x \left( \mathbf{e}^B_G \right)$ is rotated to the quasi-internal frame $\tau_x \left( \mathbf{e}^B_I \right)$. Using Eq. (24), the right-most term of Eq. (49) is
\[
\frac{\partial}{\partial \theta_x} (S) = \frac{\partial}{\partial \theta_x} \left( c_x^B (s_x^A|s_x^B) + c_y^B (p_y^A|p_y^B) + c_z^B (p_z^A|p_z^B) + c_x^B (s_x^A|p_x^B) + c_y^B (s_y^A|p_y^B) + c_z^B (s_z^A|p_z^B) \right) \\
+ \frac{c_x^B}{\partial \theta_x} (p_x^A|s_x^B) + \frac{c_y^B}{\partial \theta_x} (p_y^A|s_y^B) + \frac{c_z^B}{\partial \theta_x} (p_z^A|s_z^B) \\
= \frac{c_x^A}{\partial \theta_x} (p_x^B) (s_x^A|s_x^B) + \frac{c_y^A}{\partial \theta_x} (p_y^B) (s_y^A|s_y^B) + \frac{c_z^A}{\partial \theta_x} (p_z^B) (s_z^A|s_z^B) \\
+ \frac{c_x^A}{\partial \theta_x} (p_x^B) (s_x^A|p_x^B) + \frac{c_y^A}{\partial \theta_x} (p_y^B) (s_y^A|p_y^B) + \frac{c_z^A}{\partial \theta_x} (p_z^B) (s_z^A|p_z^B) \\
= \frac{c_x^A}{\partial \theta_x} (p_x^B) (s_x^A|p_x^B) + \frac{c_y^A}{\partial \theta_x} (p_y^B) (s_y^A|p_y^B) + \frac{c_z^A}{\partial \theta_x} (p_z^B) (s_z^A|p_z^B) \\
+ \frac{c_x^A}{\partial \theta_x} (p_x^B) (s_x^A|p_x^B) \\
= \frac{c_x^A}{\partial \theta_x} \left[ \tau_x (e^B)_x \right] (p_x^A|p_x^B) + \frac{c_y^A}{\partial \theta_x} \left[ \tau_y (e^B)_y \right] (p_y^A|p_y^B) + \frac{c_z^A}{\partial \theta_x} \left[ \tau_z (e^B)_z \right] (p_z^A|p_z^B) \\
+ \frac{c_x^A}{\partial \theta_x} \left[ \tau_x (e^B)_x \right] (s_x^A|p_x^B). \\
\]

Torque along the \( y \) and \( z \) directions are solved similarly.
V. Rotation Matrix

The overlap integral Eq. (24) is solved in the quasi-internal local frame. In this section, we show how the global coefficients $c_{xG}, c_{yG}, c_{zG}$ are transformed to the quasi-internal coefficients $c_{xI}, c_{yI}, c_{zI}$. The global and quasi-internal frames are shown below:

The global frame has basis $e_x^G = (1,0,0), e_y^G = (0,1,0), e_z^G = (0,0,1)$. The quasi-internal frame has the basis $e_x^I, e_y^I, e_z^I$ that we must solve for.

Suppose atom $A$ and atom $B$ are located at $x_A, y_A, z_A$ and $x_B, y_B, z_B$, respectively. Let $x = x_B - x_A$ and similarly for $y$ and $z$. The interatomic distance is $r = \sqrt{x^2 + y^2 + z^2}$. Since the $z_I$ axis lies along this interatomic axis, define the $e_z^I = \left(\frac{x}{r}, \frac{y}{r}, \frac{z}{r}\right)$. We choose $e_x^I$ such that $e_x^I \cdot e_z^I = 0$, i.e. $e_x^I$ and $e_z^I$ are orthogonal. One choice is $e_x^I = N \left(-\frac{y}{r}, \frac{x}{r}, 0\right)$, where $N$ is the normalizing factor $N = \frac{r}{\sqrt{x^2 + y^2}}$. Finally, we choose $e_y^I = e_z^I \times e_x^I$ so that all basis will be mutually orthogonal.

Having solved $e_x^I, e_y^I, e_z^I$, the rotation matrix $R_i$ is given as
The global coefficients are related to the quasi-internal coordinates by

\[ c_I = R_I c_G. \]  

Note that the partial derivatives in previous sections are all elements of the rotation matrix:

\[ R_I = \begin{pmatrix} \frac{\partial x_I}{\partial x_G} & \frac{\partial x_I}{\partial y_G} & \frac{\partial x_I}{\partial z_G} \\ \frac{\partial y_I}{\partial x_G} & \frac{\partial y_I}{\partial y_G} & \frac{\partial y_I}{\partial z_G} \\ \frac{\partial z_I}{\partial x_G} & \frac{\partial z_I}{\partial y_G} & \frac{\partial z_I}{\partial z_G} \end{pmatrix}. \]
References
