# A Simple Electron-Density Based Force Field Model for High-Energy Interactions between Atoms and Molecules 

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#### Abstract

In high-energy molecular dynamics or Monte Carlo simulations, standard force fields optimized for simulations at ambient temperatures are inadequate. This is largely because their repulsive parts have been regarded as not very significant, even well below zero interaction energies. It is, therefore, not obvious which force fields to resort to for simulating hot gases or plasmas. A force field model that uses the electronic densities of noninteracting atoms or molecules within the pair approximation is introduced. We start by deriving a naïve model that neglects any exchange and correlation effects between the electronic clouds and then correct this model by adding a term calibrated from ab initio calculations using the $\operatorname{CCSD}(\mathrm{T}) / \mathrm{cc}-\mathrm{pVTZ}$ level of theory. The resulting expression for this term can be regarded as a simple exchange-correlation function. We compare the results for the repulsive part of the potential energy hypersurfaces with the force fields commonly used on some dimers of small molecules.


## - INTRODUCTION

For more than 50 years, a diverse array of force field models has emerged to compute interaction energies between molecules, not least with the aim of circumventing computationally demanding quantum chemical methods, such as $a b$ initio, DFT, or semiempirical calculations, which strive to approximate the many-body Schrödinger equation. For nonreactive systems, these force fields typically comprise four key components:

Bond stretching and contractions: This involves a summation of harmonic oscillator terms to describe the stretching and contractions of bonds within a molecule.
Bond bending: Another summation of harmonic oscillator terms is employed to capture the bending of bonds in the molecular structure.
Rotations of dihedral angles: A summation is utilized to describe the rotations of dihedral angles within the molecule.
Coulomb energies and nonbonding interactions: This component involves a summation of Coulomb energies and other long-range interactions. It is often expressed as a combination of partial charges and a Lennard-Jonesstyled potential between all pairs of atoms that do not share any of the characteristics outlined in the first three components.
Utilizing such force field models enables large-scale calculations in Molecular Dynamics (MD), employing classical physics to solve Newton's equations of motion. This approach proves indispensable, especially when considering the computational limitations associated with more fundamental
quantum mechanics-derived methods. Prominent examples of these force fields include OPLS, ${ }^{1}$ CHARMM, ${ }^{2}$ UFF, ${ }^{3}$ AMBER, ${ }^{4}$ MMFF94, ${ }^{5-9}$ among numerous others. The parametrization strategy of force field models varies; for instance, MMFF94 combines experimental and computational data from the Cambridge Structural Database (CSD) and MP2/6-31G* calculations. ${ }^{10-24}$ Explorations into alternatives for the $r^{-12}$ term in the Lennard-Jones-type potential have been made such as replacing it with an $\exp (-C r)$ term (Buckingham potential). ${ }^{25}$

An important part of the quality of a force field model is the transferability. The interchangeability of the parameters of the atom classes for different molecules should be easy and/or accurate, since expecting nonexperts to design new accurate force field models for arbitrary molecules is an unrealistic expectation. Using quantum mechanical calculations to improve transferability and other features of the models is still an ongoing topic of research. ${ }^{26}$

In the pursuit of creating a universal molecular force field model, our approach involves deriving two-body interaction energies between molecules solely from their electronic densities. Initially, we make a simple assumption by considering the electronic densities of all molecules in the

[^0]
system as being independent of each other. Subsequently, we refine this assumption by introducing an exchange and correlation function based on the separated densities. This correction is inspired by the foundational concepts put forth by Hohenberg and Kohn, ${ }^{27}$ aiming to universally rectify the inaccuracies inherent in this naive assumption.
Formulating the problem for a simple system involving just two atoms, where their electronic densities are represented by some linear combination of $s$-type Gaussian functions, can be solved by using exact expressions. Prior studies have demonstrated that expanding electronic densities with primitive Hermite Gaussian functions can effectively capture Coulomb and exchange-repulsion energies between interacting molecules. This concept is employed in the Gaussian Electrostatic Model (GEM) by Cisneros et al. ${ }^{28-30}$ Other molecular force fields developed from first principles, utilizing parameters derived from accurate $a b$ initio data, include MB-$\mathrm{Pol}^{31-35}$ and the Effective Fragment Potential (EFP) method, ${ }^{36-43}$ with the latter also being an electron densitybased force field.

This study introduces a comprehensive formula for incorporating terms up to the $K^{\text {th }}$ order approximation for exchange and correlation correction. This is achieved through successive applications of the Laplace operator, resulting in a formula that eschews the use of inverse power law terms. Instead, it relies on linear combinations of expressions that function as noninteracting electron density functionals. In our preliminary numerical tests, this approach has demonstrated superior accuracy compared with several commonly used force field models, particularly in high-energy interactions when referencing $a b$ initio calculated results. Such high energy interactions are important when surfaces are subjeted to hot particles, like in plasma-wall modeling but can also occur in the liquid state when unfavorable orientations between molecules are forced by confined spaces or other constraints.
The Methods section outlines how we model the electronic density of each molecule using data derived from quantum mechanical calculations and details the calibration process for our exchange and correlation potential. In the Results section, we present a comparative analysis of our findings for different molecules against established force field models. Finally, the Conclusion section highlights the key takeaways from our study.

## - THEORY AND FORMULATION

The electronic wave function of a system AB , which consists of two molecules with a total of $N$ electrons and $M$ nuclei, $\psi_{\mathrm{AB}} \in H^{2}\left(\mathbb{R}^{3 N}\right)$, can be calculated through the timeindependent Schrödinger equation by solving the eigenvalue problem of its well-known Hamiltonian:

$$
\begin{align*}
\hat{H}_{\mathrm{AB}} \psi_{\mathrm{AB}}= & \sum_{n=1}^{N}\left(-\frac{1}{2} \nabla_{r_{n}}^{2} \psi_{\mathrm{AB}}+\sum_{n^{\prime}>n}^{N} \frac{\psi_{\mathrm{AB}}}{\left\|r_{n}-r_{n^{\prime}}\right\|}\right. \\
& \left.-\sum_{m=1}^{M} \frac{Z_{m} \psi_{\mathrm{AB}}}{\left\|r_{n}-R_{m}\right\|}\right)+\sum_{m=1}^{M} \sum_{m^{\prime}>m}^{M} \frac{Z_{m} Z_{m^{\prime}} \psi_{\mathrm{AB}}}{\left\|R_{m}-R_{m^{\prime}}\right\|} \tag{1}
\end{align*}
$$

where $r_{n}$ and $R_{m}$ denote the Cartesian coordinates of the electrons and nuclei respectively, $Z_{m}$ the atomic numbers of the atoms, and $\hat{H}_{\mathrm{AB}}: H^{2}\left(\mathbb{R}^{3 N}\right) \rightarrow H^{2}\left(\mathbb{R}^{3 N}\right)$ is the Hamiltonian acting on the combined system. The wave functions of the two
noninteracting molecules are $\psi_{A} \in H^{2}\left(\mathbb{R}^{3 N_{A}}\right)$ and $\psi_{\mathrm{B}} \in H^{2}\left(\mathbb{R}^{3 N_{\mathrm{B}}}\right)$, where $N_{A}$ and $N_{B}$ are the number of electrons in each molecule $\left(N_{\mathrm{A}}+N_{B}=N\right)$. The respective noninteracting Hamiltonian operators are $\hat{H}_{\mathrm{A}}: H^{2}\left(\mathbb{R}^{3 N_{\mathrm{A}}}\right) \rightarrow H^{2}\left(\mathbb{R}^{3 N_{\mathrm{A}}}\right)$ and $\hat{H}_{\mathrm{B}}: H^{2}\left(\mathbb{R}^{3 N_{\mathrm{B}}}\right) \rightarrow H^{2}\left(\mathbb{R}^{3 N_{\mathrm{B}}}\right)$.

In the so-called supermolecular approach, the interaction energy between A and B is defined as the difference in the total energy of the bonded system and the total energies of the separated molecules. In other words:

$$
\begin{equation*}
\Delta E_{\mathrm{AB}}=\left\langle\psi_{\mathrm{AB}}\right| \hat{H}_{\mathrm{AB}}\left|\psi_{\mathrm{AB}}\right\rangle-\left\langle\psi_{\mathrm{A}}\right| \hat{H}_{\mathrm{A}}\left|\psi_{\mathrm{A}}\right\rangle-\left\langle\psi_{\mathrm{B}}\right| \hat{H}_{\mathrm{B}}\left|\psi_{\mathrm{B}}\right\rangle \tag{2}
\end{equation*}
$$

We now derive an expression of this interaction energy for a naive model, which rests on the assumption that the electrons of each molecule are independent of any electrons that do not belong to the same molecule. That means that the wave function of the combined system equals the product of the wave functions of the separated molecules:

$$
\begin{equation*}
\psi_{A B}^{\text {Naive }}\left(Q_{A}, Q_{B}\right)=\psi_{A}\left(Q_{A}\right) \psi_{B}\left(Q_{B}\right) \tag{3}
\end{equation*}
$$

where $Q_{\mathrm{A}} \in \mathbb{R}^{3 N_{\mathrm{A}}}$ and $Q_{\mathrm{B}} \in \mathbb{R}^{3 N_{\mathrm{B}}}$ are the coordinates of the electrons of molecules $A$ and $B$, respectively. One immediate consequence of this assumption is that the electrons in the combined system are not modeled as indistinguishable particles, but rather as semi-indistinguishable particles (only if a pair of electrons "belong" to the same molecule they are modeled indistinguishably). The interaction energy for this naïve model is calculated via the following difference:

$$
\begin{equation*}
\Delta E_{\mathrm{AB}}^{\text {Naiive }}=\left\langle\psi_{\mathrm{AB}}^{\text {Naïve }}\right| \hat{H}_{\mathrm{AB}}\left|\psi_{\mathrm{AB}}^{\text {Naïve }}\right\rangle-\left\langle\psi_{\mathrm{A}}\right| \hat{H}_{\mathrm{A}}\left|\psi_{\mathrm{A}}\right\rangle-\left\langle\psi_{\mathrm{B}}\right| \hat{H}_{\mathrm{B}}\left|\psi_{\mathrm{B}}\right\rangle \tag{4}
\end{equation*}
$$

While $\psi_{\mathrm{AB}}^{\text {Naive }}$ is simple to calculate if $\psi_{\mathrm{A}}$ and $\psi_{\mathrm{B}}$ are known, it lacks two properties that the exact wave function $\psi_{\mathrm{AB}}$ must satisfy, namely the wave function is not (fully) antisymmetric (only interchanging the coordinates of electrons belonging to the same molecule will satisfy the antisymmetry condition, provided that $\psi_{\mathrm{A}}$ and $\psi_{\mathrm{B}}$ are exact wave functions of their respective molecules) nor is it guaranteed that $\psi_{\mathrm{AB}}^{\mathrm{Naive}}$ is an eigenfunction of $\hat{H}_{A B}$ (in most cases it will not be). We partition this interaction energy (eq 4) into three components: Electron-electron, electron-nuclei, and nuclei-nuclei interaction energy components between electrons/nuclei that do not belong to the same molecule $\left(\Delta E_{\mathrm{AB}}^{\mathrm{EE}}, \Delta E_{\mathrm{AB}}^{\mathrm{EN}}\right.$ and $\Delta E_{\mathrm{AB}}^{\mathrm{NN}}$, respectively):

$$
\begin{equation*}
\Delta E_{\mathrm{AB}}^{\mathrm{Naïve}}=\Delta E_{\mathrm{AB}}^{\mathrm{EE}}+\Delta E_{\mathrm{AB}}^{\mathrm{EN}}+\Delta E_{\mathrm{AB}}^{\mathrm{NN}} \tag{5}
\end{equation*}
$$

This naïve model can be quite appealing for systems with a modestly large number of electrons since the terms shown in eq 5 consist only of integrals and/or sums of the electron densities of the separated molecules and the .. Cartesian coordinates of the atoms, thus, making the naive model scalable. The analytical expressions of these terms are

$$
\begin{align*}
& \Delta E_{\mathrm{AB}}^{\mathrm{EE}}=\int_{\mathbb{R}^{3}} \int_{\mathbb{R}^{3}} \frac{\rho_{\mathrm{A}}(r) \rho_{\mathrm{B}}\left(r^{\prime}\right)}{\left\|r-r^{\prime}\right\|} \mathrm{d} r \mathrm{~d} r^{\prime}  \tag{6a}\\
& \Delta E_{\mathrm{AB}}^{\mathrm{EN}}=-\int_{\mathbb{R}^{3}}\left(\sum_{m=1}^{M_{\mathrm{B}}} \frac{Z_{m}^{\mathrm{B}} \rho_{\mathrm{A}}(r)}{\left\|r-R_{m}^{\mathrm{B}}\right\|}+\sum_{m=1}^{M_{\mathrm{A}}} \frac{Z_{m}^{\mathrm{A}} \rho_{\mathrm{B}}(r)}{\left\|r-R_{m}^{\mathrm{A}}\right\|}\right) \mathrm{d} r \tag{6b}
\end{align*}
$$

$$
\begin{equation*}
\Delta E_{\mathrm{AB}}^{\mathrm{NN}}=\sum_{m=1}^{M_{\mathrm{A}}} \sum_{m^{\prime}=1}^{M_{\mathrm{B}}} \frac{Z_{m}^{\mathrm{A}} Z_{m^{\prime}}^{\mathrm{B}}}{\left\|R_{m}^{\mathrm{A}}-R_{m^{\prime} \|}^{\mathrm{B}}\right\|} \tag{6c}
\end{equation*}
$$

where $R_{m}^{\mathrm{A}}$ and $R_{m}^{\mathrm{B}}$ denote the Cartesian coordinates of the nuclei of the molecule, and $\rho_{\mathrm{A}}$ and $\rho_{\mathrm{B}}$ are the electron densities of the molecules A and B , respectively, when they do not interact with one another. The numbers $M_{\mathrm{A}}$ and $M_{\mathrm{B}}$ denote the number of atoms each molecule contains $\left(M=M_{\mathrm{A}}+M_{\mathrm{B}}\right)$.

Despite its convenience, this naive model is unlikely to provide accurate results since the naïve wave function (eq 3) is incorrect for the reasons mentioned above. To address this, we add to the naive model an exchange and correlation interaction energy term

$$
\begin{equation*}
\Delta E_{\mathrm{AB}}^{\mathrm{XC}}: W^{2 K, 1}\left(\mathbb{R}^{3}\right) \times W^{2 K, 1}\left(\mathbb{R}^{3}\right) \rightarrow \mathbb{R} \tag{7}
\end{equation*}
$$

such that

$$
\begin{equation*}
\Delta E_{\mathrm{AB}}=\Delta E_{\mathrm{AB}}^{\mathrm{Naive}}\left(\rho_{\mathrm{A}}, \rho_{\mathrm{B}}\right)+\Delta E_{\mathrm{AB}}^{\mathrm{XC}}\left(\rho_{\mathrm{A}}, \rho_{\mathrm{B}}\right) \tag{8}
\end{equation*}
$$

where $W^{k, p}$ denotes a Sobolev space in the usual way. We now prove that the correction term $\Delta E_{\mathrm{AB}}^{\mathrm{XC}}$ does indeed exist by resorting to the Hohenberg-Kohn (HK) theorem. From a direct application of the HK theorem, we know that the interaction energy in eq 3 can be written in any case as the following functional:

$$
\begin{equation*}
\Delta E_{\mathrm{AB}}\left(\rho_{\mathrm{AB}}, \rho_{\mathrm{A}}, \rho_{\mathrm{B}}\right)=E_{\mathrm{AB}}\left(\rho_{\mathrm{AB}}\right)-E_{\mathrm{A}}\left(\rho_{\mathrm{A}}\right)-E_{\mathrm{B}}\left(\rho_{\mathrm{B}}\right) \tag{9}
\end{equation*}
$$

thus, all we are left to do is to show that $\rho_{\mathrm{A}}$ and $\rho_{\mathrm{B}}$ can be mapped to $E_{\mathrm{AB}}$. Estimating $\rho_{\mathrm{AB}}$ by simply knowing $\rho_{\mathrm{A}}$ and $\rho_{\mathrm{B}}$ is likely to be problematic in many cases, especially in cases where two atoms of different molecules are placed at short distances of each other. Since the HK theorem tells us that the external potentials of $\psi_{\mathrm{A}}$ and $\psi_{\mathrm{B}}$ are functionals of $\rho_{\mathrm{A}}$ and $\rho_{\mathrm{B}}$, respectively, it is possible to map the two electron densities to a set with the Cartesian coordinates and atomic numbers of the atoms of both molecules, which is all information required to fully describe the Hamilton operator $\hat{H}_{A B}$ of two molecules interacting with each other (eq 1).
In essence, this means that it is possible to map the electronic densities of the separated molecules to the interaction energy, as from the HK theorem it follows that the maps $\rho_{\mathrm{A}} \longmapsto E_{\mathrm{A}}$ and $\rho_{\mathrm{A}} \longmapsto E_{\mathrm{B}}$ exist. Since $\rho_{\mathrm{A}}$ and $\rho_{\mathrm{B}}$ can be mapped to their respective external potentials, they can also be mapped to the Cartesian coordinates and atomic numbers. Therefore, the pair can also be mapped to the Hamiltonian operator of the interacting system:

$$
\begin{equation*}
\left(\rho_{\mathrm{A}}, \rho_{\mathrm{B}}\right) \mapsto \widehat{H}_{\mathrm{AB}} \tag{10}
\end{equation*}
$$

Thus, it is also possible to map the pair of electronic densities to the ground state energy of the interacting system (the smallest eigenvalue of $\hat{H}_{\mathrm{AB}}$ ), that is,

$$
\begin{equation*}
\left(\rho_{\mathrm{A}}, \rho_{\mathrm{B}}\right) \mapsto E_{\mathrm{AB}} . \tag{11}
\end{equation*}
$$

While we have shown that it is possible to map the two noninteracting molecular electron densities to the energy of the interacting system (eq 9), the same cannot be stated for mapping the noninteracting densities to the electronic density of the interacting system. The reason is that the map $\left(\rho_{\mathrm{A}}, \rho_{\mathrm{B}}\right) \longmapsto \rho_{\mathrm{AB}}$ does not exist in the case of degeneracies with more than one ground state of the interacting system $(A B$
). Furthermore, using the same argument but for the separated molecules instead, it also follows that (globally) mapping the electronic density of the interacting system $\rho_{\mathrm{AB}}$ to the electronic densities of the separated molecules $\rho_{\mathrm{A}}$ and $\rho_{\mathrm{B}}$ (or in other words $\left.\rho_{\mathrm{AB}} \longmapsto\left(\rho_{\mathrm{A}}, \rho_{\mathrm{B}}\right)\right)$ is normally not possible either since one or both of the separated molecules may also have degenerate ground states.

Thus, far we have shown that $\Delta E_{\mathrm{AB}}$ can be written as a functional of the pair $\left(\rho_{\mathrm{A}}, \rho_{\mathrm{B}}\right)$. We now try to provide an expression for it via a heuristic approach where we separate $\Delta E_{\mathrm{AB}}^{\mathrm{XC}}$ into electron-electron and electron-nuclei interaction components. In each of the terms, we use a $K^{\text {th }}$ order approximation requiring the fitting of $2(K+1)$ parameters with respect to reliable experimental data, accurate (yet computationally demanding) $a b$ initio calculations or a combination of both. The parameters are the weights of different functionals of the electronic densities of the noninteracting molecules. $\Delta E_{\mathrm{AB}}$ is then defined as

$$
\begin{align*}
\Delta E_{\mathrm{AB}}^{\mathrm{XC}}\left(\rho_{\mathrm{A}}, \rho_{\mathrm{B}}\right)= & \sum_{k=0}^{K}\left(a_{k} \mathrm{XC}_{\mathrm{AB}}^{\mathrm{EE}(k)}\left(\rho_{\mathrm{A}}, \rho_{\mathrm{B}}\right)\right. \\
& \left.+b_{k} \mathrm{XC}_{\mathrm{AB}}^{\mathrm{EN}(k)}\left(\rho_{\mathrm{A}}, \rho_{\mathrm{B}}\right)\right) \tag{12}
\end{align*}
$$

with $a_{0}, \ldots, a_{K} \in \mathbb{R}$ and $b_{0}, \ldots, b_{K} \in \mathbb{R}$ being the optimized parameters and:

$$
\begin{align*}
\mathrm{XC}_{\mathrm{AB}}^{\mathrm{EE}(k)}\left(\rho_{\mathrm{A}}, \rho_{\mathrm{B}}\right)= & \int_{\mathbb{R}^{3}} \int_{\mathbb{R}^{3}} \frac{\rho_{\mathrm{A}}(r) \nabla_{r^{\prime}}^{2 k} \rho_{\mathrm{B}}\left(r^{\prime}\right)}{\left\|r-r^{\prime}\right\|} \mathrm{d} r \mathrm{~d} r^{\prime}  \tag{13a}\\
\mathrm{XC}_{\mathrm{AB}}^{\mathrm{EN}(k)}\left(\rho_{\mathrm{A}}, \rho_{\mathrm{B}}\right)= & \int_{\mathbb{R}^{3}}\left(\sum_{m=1}^{M_{\mathrm{B}}} \frac{Z_{m}^{\mathrm{B}} \nabla^{2 k} \rho_{\mathrm{A}}(r)}{\left\|r-R_{m}^{\mathrm{B}}\right\|}\right. \\
& \left.+\sum_{m=1}^{M_{\mathrm{A}}} \frac{Z_{m}^{\mathrm{A}} \nabla^{2 k} \rho_{\mathrm{B}}(r)}{\left\|r-R_{m}^{\mathrm{A}}\right\|}\right) \mathrm{d} r \tag{13b}
\end{align*}
$$

The operator $\nabla^{2 k}: W^{2 k, 1}\left(\mathbb{R}^{3}\right) \rightarrow L^{1}\left(\mathbb{R}^{3}\right)$ used in eq 13 a and 13 b is shorthand notation for applying the Laplace operator $k$ consecutive times, thus, if $k=0$ the operand is unchanged. Restricting each term of our functional in eq 13a to even numbered derivatives stemming from consecutive applications of the Laplace operator guarantees (as can be seen from integration by parts) that interchanging the labels of $\rho_{\mathrm{A}}$ and $\rho_{\mathrm{B}}$ does not affect the result of the integral, that is,

$$
\begin{equation*}
\mathrm{XC}_{\mathrm{AB}}^{\mathrm{EE}(k)}\left(\rho_{\mathrm{A}}, \rho_{\mathrm{B}}\right)=\mathrm{XC}_{\mathrm{BA}}^{\mathrm{EE}(k)}\left(\rho_{\mathrm{B}}, \rho_{\mathrm{A}}\right) \tag{14}
\end{equation*}
$$

which is a necessary condition for our model since interchanging the molecules must not alter the interaction energy (eq 2).

## ■ COMPUTATIONAL METHODS

The electronic densities of elements within the first three rows of the periodic table are computed using density functional theory (DFT) and the B3LYP functional. ${ }^{44,45}$ The calculations incorporate the empirical dispersion formula GD3 ${ }^{46}$ and an Effective Core Potential (ECP) basis-set denoted as CEP31G. ${ }^{47-49}$ The electronic densities obtained from these calculations are then approximated using three s-type Gaussian functions for the ECP basis-set, and nine s-type Gaussian
functions for the full electron basis-set aug-cc-pVTZ, ${ }^{50}$ both at the same level of theory.
To account for charge redistribution in isolated monomers, Mulliken charges ${ }^{51}$ are employed. This compensation is essential for mitigating charge redistribution effects when monomers come into close contact. Notably, this model is nonpolarizable, it does not consider charge redistribution between molecules.

In ECP calculations, effective atomic numbers replace actual atomic numbers to appropriately adjust for the reduced number of electrons due to the implementation of Effective Core Potentials. Further details, including the methodology for compensating for charge redistribution, can be found in the Supporting Information.

Representing the electronic densities of isolated molecules as linear combinations of s-type Gaussian basis functions, whether atom-centered or not, facilitates the derivation of exact closedform solutions for the integrals presented in eqs $6 a, 6 b, 13 a$, and 13 b . The exact expressions for these terms, up to order 2 , are provided in the Supporting Information. This approach simplifies the computation of integrals, offering precise solutions for the given equations. The Supporting Information contains more comprehensive details and expressions.

The exchange and correlation functional described in eq 12 is fine-tuned against Coupled Cluster Singles and Doubles (CCSD) calculations, ${ }^{52-55}$ including triple excitations (CCSD(T)), ${ }^{55,56}$ specifically for water dimers in different conformations. To evaluate the generalizability of this calibrated model, we applied it to predict interaction energies in neutral and anionic $\mathrm{O}_{2}$ dimer systems, with reference values obtained from restricted open (RO) shell $\operatorname{CCSD}(\mathrm{T})$ calculations ${ }^{57}$ to prevent spin contamination. All $\operatorname{CCSD}(\mathrm{T})$ calculations throughout this manuscript utilize the all-electron basis-set cc-pVTZ. ${ }^{50}$

The calibration process focuses on water dimer interactions due to their prominence in both dedicated and general force fields. Additionally, the choice of $\mathrm{H}_{2} \mathrm{O}$ is advantageous because of its small size, allowing the utilization of high-accuracy $a b$ initio methods. This convenience facilitates the generation of an ample amount of reference data necessary for fine tuning and calibrating our model. The water dimer, thus, serves as a valuable and practical benchmark for ensuring the accuracy and effectiveness of the calibration process.

A total of 10000 water dimers are used to calibrate the XC function. We separated them into what could be called non-hydrogen-bonded and hydrogen-bonded sets of 5000 configurations each. In the first one, the $\mathrm{O} \cdots \mathrm{O}$ distance is varied, and in the second one, the intermolecular $\mathrm{O} \cdots \mathrm{H}$ distance. Figure 1 shows the start and end of the first set of configurations ( $\Delta L \in[3,13], \theta \in[\pi, 3 \pi / 2])$ and Figure 2 shows the same for the second $(\Delta L \in[2,9.5], \theta \in[-\pi / 2,0])$. The config-


Figure 1. $\mathrm{H}_{2} \mathrm{O}$ dimers in "oxygen-bonded" configurations considered to determine the coefficients in the correction terms (eq 12).
urations are sampled in a $25 \times 200$ grid for the angular and the distance components, respectively.


Figure 2. $\mathrm{H}_{2} \mathrm{O}$ dimers in "hydrogen-bonded" configurations considered to determine the coefficients in the correction terms (eq 12).

For the $\operatorname{CCSD}(\mathrm{T})$ calculations for $\mathrm{O}_{2}$ dimers, the charge states neutral, cation, and dication are considered. Both molecules are placed in a colinear arrangement, and their distance is varied $(\Delta L \in[3,11])$. The lowest-energy spin states taken, for example, triplet states for isolated $\mathrm{O}_{2}$ neutral molecules), and the interatomic distance $\Delta L$ is evaluated on a grid of 300 evenly distributed points (Figure 3).


Figure 3. $\mathrm{O}_{2}$ dimer configurations.
We evaluate the interaction energies computed at the $\operatorname{CCSD}(\mathrm{T}) /$ aug-cc-pVTZ level of theory across our entire calibration data set. We contrast these reference values with the results obtained from both our calibrated models, ECP and full electron. Furthermore, we compare these energies with those from widely used and frequently cited molecular force field models. Specifically, we include GAFF, ${ }^{58}$ MMFF94S ${ }^{59}$ (using the open source OpenBabel software ${ }^{60}$ for both) Jorgensen's TIP3P water model, ${ }^{61}$ MB-Pol ${ }^{31-35}$ (using MBX ${ }^{62}$ and EFP, ${ }^{36-43}$ and the open-source library LIBEFP). ${ }^{63}$

The dependence of the accuracy on the approximation order is expressed by the Relative Absolute Errors (RAEs) of the predicted interaction energies against the $\operatorname{CCSD}(\mathrm{T})$ results on all calculations of the $\left(\mathrm{H}_{2} \mathrm{O}+\mathrm{H}_{2} \mathrm{O}\right)$ complexes:

$$
\begin{equation*}
\mathrm{RAE}_{k}=\frac{\sum_{n}\left|\Delta E_{\mathrm{AB}}^{(k)}\left(\rho_{\mathrm{A}}^{n}, \rho_{\mathrm{B}}^{n}\right)-\Delta E_{\mathrm{AB}}^{\mathrm{CCSD}(\mathrm{~T})}\left(\rho_{\mathrm{AB}}^{n}\right)\right|}{\sum_{n}\left|\Delta E_{\mathrm{AB}}^{\mathrm{CCSD}(\mathrm{~T})}\left(\rho_{\mathrm{AB}}^{n}\right)\right|} \tag{15}
\end{equation*}
$$

All the DFT and $\operatorname{CCSD}(\mathrm{T})$ calculations used in this manuscript were performed using the Gaussian 16.3 Software, ${ }^{64}$ using the High-Performance Computing (HPC) facility of the University of Innsbruck. A combination of a genetic algorithm and the Broyden-Fletcher-GoldfarbShanno (BFGS) algorithm ${ }^{65-68}$ was used for all the nonlinear least-squares optimizations, using Julia programming languagebased scripts.

## RESULTS AND DISCUSSION

The electronic densities of the elements in the first three rows of the periodic table are effectively replicated using three Gaussian functions in ECP basis-set calculations, although the approximation of the electronic densities of H and He appears coarser than that for the other atoms, as evidenced in Figure 4. This discrepancy is expected, given that the full electron density for these two elements comprises the summation of two 1s-type orbitals, dictated by the chosen basis set. Fortunately, this issue is not persistent for other elements, as


Figure 4. Comparison of the approximated radial component of the electronic densities (dashed lines) versus the respective DFT results (solid lines) for helium, lithium, oxygen, and argon atoms. Radial distances are given in Bohr.
their $2 s$ atomic orbitals inherently exhibit smoother characteristics.

The coefficients of the Gaussians for these elements are listed in the Supporting Information. Conversely, when employing a full electron basis-set, accurate reproduction of electronic densities is achieved through the utilization of nine s-type Gaussian functions for all atoms in the first three rows. It is worth noting that in contrast to the ECP scenario, the expressions fitted from full electron calculations are less accurate for very small distances to the nucleus.

Our corrected models of order six (ECP fitted) and four (full electron fitted) demonstrate commendable accuracy in replicating $a b$ initio data for energies, surpassing even established force fields, as illustrated in Figure 5. It is important to note that this comparison holds some subjectivity, primarily due to the heightened emphasis on configurations where the interaction between the water molecules in the dimers is markedly repulsive. Our objective is to cultivate a model capable of accurately reproducing such
regions, as they bear significance in simulations of systems subjected to high temperatures or large atomic kinetic energies in general.

In a broader context, the MMFF94S, EFP and MB-Pol models exhibit proficiency in maintaining accuracy at elevated interaction energies, with the latter emerging as the superior choice overall. However, even though MB-Pol generally outperforms our ECP and full electron models at lower energy interactions, it tends to overshoot at higher energies. This is expected, considering that MB-Pol employs inverse power laws for determining interaction energies. Another pivotal distinction lies in the polarizable nature of MB-Pol, necessitating an additional computational step at runtime, a feature absent in our nonpolarizable model. It is essential to recognize these nuances when considering the trade-offs between accuracy and computational efficiency in selecting an appropriate model for simulations.

We also find that for interatomic distances shorter than $3 \AA$ in the repulsive $\mathrm{O} \cdots \mathrm{O}$ reaction coordinate of the water dimer, both GAFF, TIP3P, and EFP exhibit shortcomings in reproducing the interaction energy, as depicted in Figure 6. In contrast, our ECP and full electron calibrated models, along with MMFF94S and MB-Pol, maintain accuracy even when interatomic distances are shorter than $2 \AA$. For energies below $150 \mathrm{~kJ} / \mathrm{mol}$, MB-Pol shows remarkable accuracy, outperforming both the ECP and full electron calibrated models. However, for higher energy configurations, where shorter interatomic distances appear, MB-Pol also overestimates the energies, whilst both the ECP and full electron calibrated models remain accurate. This observation highlights the strengths of our calibrated models in accurately capturing interaction energies, especially in regions with challenging interatomic distances.
An analogous inspection of hydrogen-bonded configurations in Figure 7 yields a slightly different perspective. All models except EFP demonstrate accuracy in predicting attractive regions. However, in the plotted region, only our ECP and full electron calibrated models, along with MB-Pol, accurately


Figure 5. Comparison between the interaction energies obtained from the CCSD (T)/cc-pVTZ level of theory (singlets) against the results from our corrected models and four established force field models. The data points displayed here are the same used to fit the parameter of our model.


Figure 6. Interaction energy of a water dimer in the $\mathrm{O} \cdots \mathrm{O}$ reaction coordinate shown in Figure $1(\theta=\pi)$ obtained from ab initio calculations (singlets) using $\operatorname{CCSD}(\mathrm{T}) /$ cc-pVTZ level of theory and several force field models including ours with an order six and four corrections for the ECP and full electron models, respectively. The curves of our "ECP fit" and "full electron fit" models overlap with each other.


Figure 7. Interaction energy of a water dimer in the $\mathrm{O} \cdots \mathrm{H}$ reaction coordinate shown in Figure $2(\theta=-\pi / 4)$ obtained from ab initio calculations (singlets) using $\operatorname{CCSD}(\mathrm{T}) /$ cc-pVTZ level of theory and several force field models including ours with an order six and four corrections for the ECP and full electron models, respectively.


Figure 8. Normalized error of the interaction energies for the full electron model (left panel) and ECP model (right panel) of all the configurations shown in Figure 5 as functions of the approximation order (labeled as $k$ ). The red line is a linear fit through the data points.
modeled the repulsive part. This again underscores the effectiveness of our calibrated models and of MB-Pol in capturing both attractive and repulsive interactions in hydro-gen-bonded configurations.

Figure 8 illustrates the decay of the Relative Absolute Error (RAE), as defined in eq 15 , on a double logarithmic scale. For the sixth order, the RAE stands at approximately 0.05 for the ECP fitted model. However, as orders exceed 6, the improvement in the ECP model performance decelerates. The orange line in the figure is a fit to the RAE values for orders 1 to 6 , and its slope and offset are depicted in the inset. Despite the ECP model with orders beyond six exhibiting a smaller total error, indications of overfitting start emerging beyond the sixth order. Small artifacts become noticeable near the minimum potential well of the same $\mathrm{O} \cdots \mathrm{H}$ reaction coordinate depicted in Figure 7.

Conversely, the error of our full electron model diminishes linearly on the double logarithmic scale, as shown in Figure 8. However, for orders surpassing four, unphysical oscillations manifest in the $\mathrm{O} \cdots \mathrm{H}$ reaction coordinate, as shown in Figure 7. To precisely extrapolate interaction energies along this reaction coordinate, expanding our calibration data set to include water dimer configurations with even shorter interatomic distances is imperative.

This limitation is anticipated when scrutinizing the proposed exchange and calibration functional, as depicted in Figure S1 of the Supporting Information. The higher the order of each functional in the sum, the more oscillations occur, presenting challenges in extrapolating interaction energies for specific reaction coordinates that may or may not be part of the calibration data set.

Concerning the $\mathrm{O}_{2}$ dimer systems, both our ECP and full electron calibrated models demonstrate the ability to predict
interaction energies for an $\mathrm{O}_{2}^{-}+\mathrm{O}_{2}^{-}$complex in the triplet spin state, as illustrated in Figure 9. Remarkably, despite being


Figure 9. Interaction energy of an $\mathrm{O}_{2}^{-}+\mathrm{O}_{2}^{-}$complex in the reaction coordinate shown in Figure 3 obtained from $\operatorname{CCSD}(\mathrm{T}) / \mathrm{cc}-\mathrm{pVTZ}$ level of theory and our calibrated model from neutral water dimer calculations (same level of theory) using an order six and four corrections for the ECP and full electron models, respectively. The red and gray curves practically overlap in the plot.
exclusively calibrated from neutral water dimer calculations, these models perform well for this different molecular configuration. However, for interatomic distances shorter than approximately $2.5 \AA$, the accuracy of our full electron model diminishes, while the ECP model maintains a fair degree of accuracy.
A similar conclusion is drawn by examining of $\mathrm{O}_{2}+\mathrm{O}_{2}$ complexes in an identical reaction coordinate, as depicted in Figure 10. Both models yield results identical to $a b$ initio data


Figure 10. Interaction energy of an $\mathrm{O}_{2}+\mathrm{O}_{2}$ complex in the reaction coordinate shown in Figure 3 obtained from $\operatorname{CCSD}(\mathrm{T}) /$ cc-pVTZ level of theory and our calibrated model from neutral water dimer calculations (same level of theory) using an order six and four corrections for the ECP and full electron models, respectively.
for interatomic distances larger than $2.25 \AA$, and beyond this point, the ECP calibrated model is notably more accurate. This evaluation highlights the versatility of our calibrated models in extending their predictive capabilities beyond the specific calibration set, while also showcasing the nuanced performance differences between the ECP and full electron models in certain molecular configurations.

Deficiencies due to the Limited Data Base and/or Lack of Polarizability. While our model has proven successful in replicating potential energy surfaces between monomers where no covalent bonds are formed or broken, it struggles when modeling the interaction energies within an $\left(\mathrm{O}_{2}+\mathrm{O}_{2}\right)^{-}$complex along the reaction coordinate depicted in Figure 11. Both our "ECP fit" and "full electron fit" models predict an entirely incorrect repulsive potential, in contrast with the attractive potential observed in the $a b$ initio reference


Figure 11. Interaction energy of an $\left(\mathrm{O}_{2}+\mathrm{O}_{2}\right)^{-}$complex in the $\mathrm{O} \cdots \mathrm{O}$ reaction coordinate shown in Figure 3 obtained from $\operatorname{CCSD}(\mathrm{T}) / \mathrm{cc}-$ pVTZ level of theory and our calibrated model from neutral water dimer calculations (same level of theory) using an order six and four corrections for the ECP and full electron models, respectively.
data. Notably, the full electron model exhibits a noticeably lower level of accuracy in this context.

Determining the exact reasons for these inaccuracies is challenging. The absence of reference data for interactions involving both neutral and anion species of the same molecule will play a role. Additionally, the methodology of modeling anion electron densities by simply scaling them to match the electron populations of an anion monomer might be insufficient for accurately simulating interactions with anions. Further investigation and refinement of the model in the context of anionic species are warranted to enhance its accuracy and reliability in such scenarios.

Deficiencies of the Exchange and Correlation Functional. In examining the repulsive region of the $\mathrm{O} \cdots \mathrm{H}$ reaction coordinate of the water dimers, our ECP fitted model remains accurate up to about $250 \mathrm{~kJ} / \mathrm{mol}$, whereas our full electron model maintains accuracy up to $2000 \mathrm{~kJ} / \mathrm{mol}$ (trimmed to $1000 \mathrm{~kJ} / \mathrm{mol}$ in Figure 12 for illustrative purposes) in this


Figure 12. Interaction energy of a water dimer in the $\mathrm{O} \cdots \mathrm{H}$ reaction coordinate shown in Figure $2(\theta=-\pi / 4)$ obtained from $\operatorname{CCSD}(\mathrm{T})$ / cc-pVTZ calculations and our order six and four ECP and full electron models, respectively. The interaction energies are extrapolated to shorter interatomic distances with our model.
reaction coordinate. As interatomic distances decrease, such as in the intermolecular $\Delta L_{\mathrm{O}-\mathrm{H}}$, our model encounters a point where strong, unphysical oscillations become apparent (Figure 12). Notably, for the ECP basis-set, these oscillations occur at much shorter interatomic distances.

While oscillations are also observed for our fitted model with the full electron basis-set, the precise reason is not entirely clear. Potential contributing factors include a lack of reference data with short interatomic distances, the oscillatory nature of our proposed exchange and correlation functionals at higher
orders (as seen in Figure S1 of the Supporting Information), the truncation of our exchange and correlation functional at a finite order, lack of enough reference data in high interaction energy regions, and/or the lack of polarizability in our model. Nevertheless, both our ECP and full electron fitted models accurately extend to largely repulsive regions, with the full electron model being the preferred choice for simulations with more extreme energy requirements.

## ■ CONCLUSIONS

In our study, we present a comprehensive framework for modeling intermolecular interaction energies from electron densities by using basis functions designed for atoms in the first three rows of the periodic table. We employ both ECP and full electron calculations with three and nine s-type Gaussian functions, respectively. Our approach initiates with a naive model, assuming the independent movement of electrons in each molecular clouds. A more accurate prediction is attained through a series expansion involving consecutive applications of the differential Laplace operator, interpreted as exchange and correlation interaction correction terms. Leveraging the Hohenberg-Kohn theorem, we demonstrate the existence of such a functional, requiring a relatively high-order expansion (6 or higher) for the accurate modeling of interaction energies. However, challenges arise in high-order expansions for extrapolating to extremely high interaction energy regions due to the oscillatory nature of our proposed exchange and correlation functional.
Testing our force field model, including both ECP and full electron versions, on a variety of water and oxygen dimer configurations yields accurate predictions for interaction energies within $400 \mathrm{~kJ} / \mathrm{mol}$ for the ECP case, while the full electron model displays the capability for much higher energies. Notably, our model outperforms some popular force fields in the literature, particularly in the repulsive "high-temperature" part of potential energy surfaces, especially for interaction energies below $400 \mathrm{~kJ} / \mathrm{mol}$.

While our model demonstrates efficiency, being on average 10 times slower than TIP3P for water dimer interaction energies, it remains considerably faster than the $a b$ initio methods. Challenges arise in predicting interaction energies for the $\mathrm{O}_{2}$ dimer anion, indicating that the expansion coefficients obtained at the present state of our models are not universal, emphasizing the need for careful testing. For molecular dynamics simulations requiring accurate modeling of highenergy regions of potential walls, such as in hot plasmas, the model calibrated from full electron calculations is better suited. Notably, it did not display signs of unphysical oscillations in the few high-energy extrapolation cases studied (for an order of four expansion). Conversely, our ECP-fitted model with an order six expansion proves to be superior to the full electronfitted model for lower-energy simulations, such as the ones relevant in biophysics or drug discovery.

## ■ ASSOCIATED CONTENT

## Data Availability Statement

All the data and programming scripts used to write this manuscript are freely available under a GPL-3.0 license, and can be downloaded from the GitHub repository: https:// github.com/JoseRodriguezRomero/ ElectronDensityForceModel

## (s) Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.jpca.3c06724.

Tables with all the fitted coefficients of the s-type Gaussian functions against ECP and full electron DFT calculated electron densities, exact expressions for the exchange and correlation functionals up to order two and their recursive expressions for higher order functionals, and the exchange and correlation coefficients for an order four full electron and an order six ECP models obtained from least-squares minimization against all the $a b$ initio water dimer calculations (PDF)

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## Notes

The authors declare no competing financial interest.

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