

DEGAUSS: A Novel Softcore Force Field Using Double Exponential van der Waals and Gaussian Charge for Molecular Dynamics Simulations I: Theory and Validation

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Zhen Huang, Yong Duan, Xiongwu Wu,* and Ray Luo*



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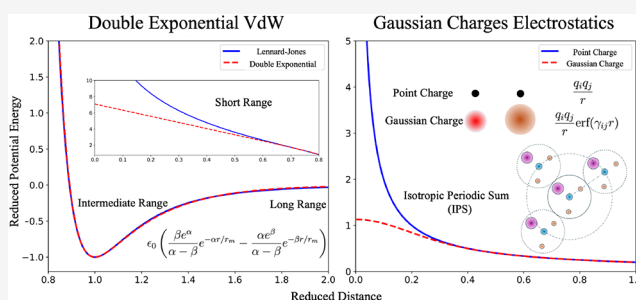


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ABSTRACT: Classical molecular force fields contain singularities in Lennard-Jones and Coulombic potentials that cause numerical challenges under extreme conditions, including transition states, high temperatures and pressures, and alchemical free energy calculations. We present DEGAUSS, a singularity-free force field framework that eliminates these divergences by replacing Lennard-Jones potentials with double exponential functions and point charges with Gaussian charge distributions, ensuring that all interactions remain finite even at zero separation. Using existing classical force field parameters as a starting point, we define DEGAUSS-specific parameters that closely resemble the behaviors of the classical force field, while avoiding numerical instabilities. Validation studies of TIP3P and OPC3 water models demonstrate excellent reproduction of thermodynamic and structural properties across diverse temperature ranges. Alanine dipeptide simulations preserve major conformational states, and protein benchmarks show structural stability consistent with that of conventional force fields. Hydration free energy calculations using alchemical methods demonstrate the absence of singularities during particle annihilation without requiring additional softcore potentials while producing results comparable to classical methods. Although the smooth functional forms increase computational costs relative to standard Lennard-Jones potentials and Coulomb potentials, DEGAUSS provides a robust framework that maintains chemical accuracy and simplifies alchemical free energy calculations.



INTRODUCTION

Molecular simulations have extended our ability to study biomolecular systems by providing atomic-resolution insights into their structure, dynamics, and thermodynamic properties.¹ At the heart of these simulations lies the calculation of the potential energies of molecular systems. While quantum mechanical methods can in principle provide exact solutions for potential energies as a function of atomic coordinates, $V(\{\vec{r}\})$, their computational costs scale poorly with system size. This limitation has led to the development of classical force fields that approximate the potential energy surface through carefully parametrized analytical functions. These force fields typically decompose the total potential energy into bonded terms that account for covalent interactions through bond stretching, angle bending, torsional potentials, and nonbonded terms that are typically described as van der Waals (vdW) and electrostatic interactions between atoms.^{2–6}

The vdW interactions are most commonly modeled by the Lennard-Jones (LJ) potential.⁷ In AMBER, this takes the following form

$$V_{\text{LJ}}(r_{ij}) = \epsilon_{ij} \left[\left(\frac{r_m}{r_{ij}} \right)^{12} - 2 \left(\frac{r_m}{r_{ij}} \right)^6 \right] \quad (1)$$

where ϵ_{ij} represents the depth of the potential well, r_{ij} is the interatomic distance between particles i and j , and r_m is the distance at which $V_{\text{LJ}}(r_m) = -\epsilon_{ij}$ is the minimum. In the simplest form, the electrostatic interactions between two point charges q_i and q_j on atoms i and j are described by Coulomb's law

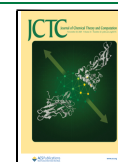
$$V_{\text{Coulomb}}(r_{ij}) = \frac{1}{4\pi\epsilon_0} \frac{q_i q_j}{r_{ij}} \quad (2)$$

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with ϵ_0 being the vacuum permittivity.

The standard formulations of classical force fields, while successful for many applications, have inherent limitations when examined through the lens of modern simulation needs. One of such limitations is the existence of singularities in the formulations that may occur when two nonbonded atoms are too close, which can happen under extreme conditions such as high pressure, high temperatures, and in transition states.

Partly because of this, alternative vdW potentials have been developed to address the specific shortcomings of the LJ formulation. For example, the repulsive r^{-12} term is known to be a poor mimic of atomic repulsion at short distances and is known to be “too steep.” Although it is generally believed that the dispersion asymptotically approaches r^{-6} at long-range, its short- and medium-range behavior is far less clear.

The presence of high-power singularity, which diverges at the rates of r^{-12} and r^{-6} , respectively, when r approaches zero, can pose potential challenges to the numerical stability of simulations. Even the widely applied Coulomb interaction suffers from an r^{-1} singularity when r approaches zero and, because it implicitly assumes point charges, exhibits short-range behavior that poorly represents atomic electrostatic interactions.

To circumvent the problems, remedies have been proposed before. For example, the Buckingham potential replaces the r^{-12} repulsion with an exponential term, yielding the form⁸

$$V_{\text{Buck}}(r) = A \exp(-Br) - \frac{C}{r^6} \quad (3)$$

where A , B , and C are the parameters governing the repulsive barrier, decay rate, and dispersion strength, respectively. The replacement of r^{-12} by an exponential function makes the repulsion term closer to the core repulsion. Yet, the singularity of the dispersion term remains. In the MMFF⁹ and AMOEBA¹⁰ force fields, a buffered 14–7 potential is employed in the form of

$$V(r) = \epsilon_0 \left(\frac{1 + \delta}{\frac{r}{r_m} + \delta} \right)^7 \left(\frac{1 + y}{\left(\frac{r}{r_m} \right)^7 + y} - 2 \right) \quad (4)$$

where ϵ_0 determines the well depth, r_m the equilibrium distance at which $V(r_m) = -\epsilon_0$, δ the dimensionless softening parameter, and y is another dimensionless parameter that controls the shape of the potential. A common theme in the works of Buckingham and Halgren was the reduction of the singularity. These alternative forms provide more physically accurate vdW representations of short-range repulsion and intermediate-range attraction.

Recent advances in electrostatic modeling have moved beyond fixed point charges through several complementary approaches to capture polarization effects. Drude oscillator models^{11,12} introduce auxiliary charged particles connected to atoms via harmonic springs, while induced dipole methods^{13–17} treat polarizability through atomic dipole moments responding to local electric fields. Among these, the polarizable Gaussian multipole (pGM) model^{17–20} employs Gaussian-shaped charge distributions to naturally capture charge penetration effects while achieving near-quantum mechanical accuracy in electrostatic interactions. Fluctuating charge models²¹ dynamically adjust atomic partial charges based on electronegativity equalization principles.

Despite their differences, a common limitation lies in their fundamental mathematical formulation. The singularities inherent in the functional forms of either vdW or electrostatic potentials or, in some cases, both, as expressed in eqs (1) and (3), can pose challenges, which can become an acute problem in alchemical transformations.^{22,23} The singularity of r^{-12} repulsion in LJ-type potentials and the r^{-1} in Coulombic interactions at $r = 0$ lead to difficulties in creation/annihilation processes. This deficiency persists across most force field variants, including many polarizable models and alternative vdW formulations. While these advanced force fields may better describe equilibrium properties and dynamics of stable molecular configurations, they inherit the same fundamental challenges for free energy calculations. Furthermore, because alchemical transformation remains one of the most efficient methods in the quantitative free energy calculations, it is highly desirable to have a method that can eliminate the singularity and accurately mimic the van der Waals and electrostatic contributions.

We propose a new approach for nonbonded interactions through what we call the DEGAUSS force field. This formula combines two innovative components: a double exponential (DE) vdW potential and Gaussian-shaped charge–charge interactions for electrostatics. The DE formulation^{24,25} builds directly on our previous studies that validated its ability to accurately reproduce LJ behavior while intrinsically possessing softcore properties that eliminate singularities when atoms overlap. This approach represents a fundamental shift from conventional r^{-12} repulsion to a more physically sensible exponential form that smoothly reaches a finite value as r approaches zero. For the electrostatic component, we employ Gaussian-shaped charge distributions that naturally capture charge penetration effects, drawing from our extensive work developing the polarizable Gaussian multipole (pGM) model,^{17,18} where this represents the monopole–monopole interaction term. Unlike point charges that create infinite potentials upon overlap, these Gaussian charge distributions yield finite interaction energies at all distances, providing a mathematically robust solution to the singularity problem. The pGM framework has been rigorously shown to achieve high accuracy in representing electrostatic interactions while remaining computationally tractable.^{17,19,20,26–32}

The key question to be addressed in this study is whether a combination of these two inherently softcore-natured potentials can successfully recover classical force field behavior while overcoming their intrinsic mathematical limitations. Specifically, we investigate whether the softcore nature of these potentials compromises their ability to accurately model biomolecular systems. This concern arises because traditional softcore potentials, while solving singularity problems, often distort the energy landscape in ways that affect structural and thermodynamic properties. Compared with the classic LJ and Coulombic potentials, both the DE vdW and Gaussian electrostatic terms involve computationally more expensive evaluations. This shortcoming is addressed through the implementation of the isotropic periodic sum (IPS) method.^{33–37} The IPS method approximates the long-range contribution of interactions beyond a cutoff by assuming an isotropic distribution of particles, dramatically reducing the computational cost while maintaining accuracy for homogeneous systems. The IPS approach is particularly well-suited for biomolecular systems in aqueous solution due to their inherent isotropy, as it assumes homogeneous environmental con-

ditions, where periodic images adopt random rather than crystalline distributions. This allows all nonbonded interactions to be evaluated by using pairwise terms with a physical cutoff distance, replacing the more computationally demanding particle-mesh Ewald methods typically required for long-range electrostatic calculations.

In the following, we first present the DEGAUSS versions of both TIP3P³⁸ and OPC3³⁹ water models. We systematically compare their ability to reproduce the energetic, thermodynamic, and kinetic properties of the original models, including the density, heat of vaporization, self-diffusion coefficient, radial distribution functions, and dielectric constant. These physical properties collectively probe both the structural and the dynamic aspects of the solvent. More complex systems are then studied to scrutinize conformational space sampling and free energy surfaces, starting with the alanine dipeptide. This small peptide serves as an essential benchmark because of its well-characterized free energy landscape with distinct minima corresponding to different backbone conformations, and its simulation provides a sensitive test of the balance between various interaction terms.⁴⁰ The next test focuses on simulations of three small proteins (PDB IDs: 1enh, 1pga, and 1ubq). These well-characterized proteins represent diverse folds: the all- α engrailed homeodomain (1ENH),⁴¹ the predominantly β protein G B1 domain (1PGA),⁴² and the mixed α/β ubiquitin (1UBQ).⁴³ These proteins allow us to evaluate how DEGAUSS performs in maintaining native structures and backbone fluctuations. The final test is a preliminary alchemical free energy calculation, in which we compute the hydration free energy of a Na⁺ ion in water. This test demonstrates one of the key advantages of DEGAUSS: the absence of singularities during particle annihilation without requiring additional softcore potentials, which are necessary in classical force fields. This validation suite specifically focuses on demonstrating that DEGAUSS can accurately reproduce classical force field behaviors, confirming that classical force field parameters can be directly adapted to DEGAUSS potentials to achieve Lennard-Jones van der Waals and point-charge electrostatic interactions with high accuracy.

METHODS

Double Exponential van der Waals Potential. The vdW interactions in DEGAUSS employ a DE potential with the form

$$V_{\text{DE}}(r) = \epsilon_0 \left(\frac{\beta e^\alpha}{\alpha - \beta} e^{-\alpha r/r_m} - \frac{\alpha e^\beta}{\alpha - \beta} e^{-\beta r/r_m} \right) \quad (5)$$

where ϵ_0 represents the potential well depth, r_m is the equilibrium distance, and α , β are the dimensionless parameters controlling the repulsive and attractive potential steepness. The first exponential term dominates at short distances, providing quantum-mechanically justified repulsion, while the second term captures dispersion attraction. The potential minimum occurs at $r = r_m$ with depth ϵ_0 , matching conventional force field parametrization schemes.

Gaussian Charge Electrostatics. The electrostatic component of DEGAUSS utilizes the Gaussian-distributed charges that share the formula of charge distribution function as well as the charge–charge interaction energies with the polarizable Gaussian multipole (pGM)¹⁷ framework. Here, each charge distribution ρ is with a radius $1/\gamma$ and centered at position $\vec{R}$:

$$\rho(\vec{r}; \vec{R}) = q \left(\frac{\gamma}{\sqrt{\pi}} \right)^3 \exp(-\gamma^2 |\vec{r} - \vec{R}|^2) \quad (6)$$

where γ here corresponds to the β in the work describing pGM.¹⁷ With such formulation, the charge–charge interaction can be written in the form of an error function

$$V_{\text{Gauss}}(r) = \frac{q_i q_j}{r} \text{erf}(\gamma_{ij} r) \quad (7)$$

where $\gamma_{ij} = \frac{\gamma_i \gamma_j}{\sqrt{\gamma_i^2 + \gamma_j^2}}$ combines atom-specific width parameters

$1/\gamma_i$, q_i and q_j are the partial charges of atoms i and j . The error function accounts for the charge penetration effects with penetration depth γ_{ij}^{-1} and smoothly transitions to pure Coulombic behavior at $r \gg \gamma_{ij}^{-1}$. With the error function, the atoms can be close to each other while still maintaining finite electrostatic interactions, eliminating the singularity problem that plagues point-charge models.

Isotropic Periodic Sum Method Implementation. The isotropic periodic sum (IPS) method is an image-based method, similar to lattice-based methods like Ewald sums. The difference is that the IPS method employs isotropic periodic images to represent remote structures. Under the IPS framework, the potential energy is approximated as the pairwise potential within the cutoff distance plus the IPS potential ϕ^{IPS} .

$$E_i = \frac{1}{2} \sum_j \epsilon(r_{ij}) \approx \phi^{\text{IPS}}(0, r_c) + \frac{1}{2} \sum_{r_{ij} < r_c} (\epsilon(r_{ij}) + \phi^{\text{IPS}}(r_{ij}, r_c)) \quad (8)$$

where E_i is the energy of particle i , $\epsilon(r_{ij})$ is the pair potential between particles i and j , r_c is the cutoff distance, and $\phi^{\text{IPS}}(r_{ij}, r_c)$ represents the long-range correction from the isotropic periodic images.

The IPS algorithm has been extensively developed and has shown superior behavior as a good alternative to Ewald methods. In particular, it scales linearly with system size and avoids the need for reciprocal space calculations. In addition, in recent IPS publications, we have established an easy way to derive the IPS potential for different types of potential energy functionals.

For the DEGAUSS force field, the IPS formulation has been derived before. The DE IPS potential is²⁴

$$\epsilon_{\text{DE}}^{\text{IPS}}(r, r_c) = \begin{cases} \epsilon_0 [A(r, r_c) - B(r, r_c)] & r \leq r_c \\ 0 & r > r_c \end{cases} \quad (9)$$

where

$$A(r, r_c) = \frac{\beta e^\alpha}{\alpha - \beta} \left[\exp\left(-\alpha \frac{r}{r_m}\right) + \Phi_{\text{E}}^{\text{IPS}}\left(r, r_c, \frac{\alpha}{r_m}\right) \right] \quad (10)$$

$$B(r, r_c) = \frac{\alpha e^\beta}{\alpha - \beta} \left[\exp\left(-\beta \frac{r}{r_m}\right) + \Phi_{\text{E}}^{\text{IPS}}\left(r, r_c, \frac{\beta}{r_m}\right) \right] \quad (11)$$

The IPS potential derived for the exponential is

$$\phi_{\text{E}}^{\text{IPS}}(r, r_c, \kappa) = e^{\kappa(r-2r_c)} + \frac{12e^{-\kappa r_c}}{\kappa^2 r_c^2} + \frac{6e^{-2\kappa r_c}}{\kappa^3 r_c^3} \quad (12)$$

And for the Gaussian electrostatics, we have published how we deal with Gaussian multipoles, where the Gaussian charge is equivalent to the zeroth-order multipole, for which the IPS potential is shown below⁴⁴

$$\epsilon_G^{\text{IPS2}}(r, r_c) = \frac{1}{r} \text{erf}(\gamma r) + A_2 + B_2 r^2 + C_2 r^4 + D_2 r^6 \quad (13)$$

where the coefficients A_2 , B_2 , C_2 , and D_2 are defined as

$$A_2 = -\frac{1}{48r_c} \left(105 \text{erf}(\gamma r_c) - \frac{114\gamma r_c + 44\gamma^3 r_c^3 + 8\gamma^5 r_c^5}{\sqrt{\pi}} e^{-\gamma^2 r_c^2} \right) \quad (14)$$

$$B_2 = \frac{1}{48r_c^3} \left(105 \text{erf}(\gamma r_c) - \frac{210\gamma r_c + 108\gamma^3 r_c^3 + 24\gamma^5 r_c^5}{\sqrt{\pi}} e^{-\gamma^2 r_c^2} \right) \quad (15)$$

$$C_2 = -\frac{1}{48r_c^5} \left(63 \text{erf}(\gamma r_c) - \frac{126\gamma r_c + 84\gamma^3 r_c^3 + 24\gamma^5 r_c^5}{\sqrt{\pi}} e^{-\gamma^2 r_c^2} \right) \quad (16)$$

$$D_2 = \frac{1}{48r_c^7} \left(15 \text{erf}(\gamma r_c) - \frac{30\gamma r_c + 20\gamma^3 r_c^3 + 8\gamma^5 r_c^5}{\sqrt{\pi}} e^{-\gamma^2 r_c^2} \right) \quad (17)$$

Parametrization Strategies. A comprehensive force field development would require extensive simulations and validation against diverse experimental data, which are beyond our current scope. Therefore, our primary goal in the current work is to demonstrate that DEGAUSS is capable of reproducing classical force fields while reducing their mathematical singularities. We propose several targeted parametrization strategies.

For the vdW interactions, we adopt a systematic fitting approach where we preserve the well depth (ϵ_0) and location (r_m) from the original LJ potential. The dimensionless parameters α and β of the DE potential are determined by fitting to the LJ potential so that the DE can reasonably reproduce the vdW energy of the force field for the range that is near $r = r_m$. For example, in the case of water molecules, when we fit to the LJ potential in the distance range from $0.7r_m$ to $3.0r_m$, we obtain $\alpha = 18.17$ and $\beta = 3.65$. We use $\alpha = 18.17$ and $\beta = 3.65$ for all LJ potentials for consistency. This approach ensures that the resulting potential maintains appropriate repulsive behavior while preserving the critical intermolecular interactions necessary for stable molecular dynamics simulations and accurate conformational sampling.

For the Gaussian electrostatic component, in the present initial stage of development, we employ a uniform radius parameter ($1/\gamma$) for all atoms for simplicity. This uniform treatment serves as a baseline that can be refined in future work to include atom-specific radii when evidence warrants.

Simulation Details. We conducted a hierarchical validation protocol, beginning with liquid water. Our initial test employed a cubic box containing 512 TIP3P water

molecules, followed by an identical setup using the OPC3 water model. For both systems, we evaluated thermodynamic (density, heat of vaporization, dielectric constant, heat capacity at constant pressure, thermal expansion coefficient, isothermal compressibility) and kinetic (self-diffusion coefficient) properties under both NVT and NPT ensembles at 298 K. Simulations were performed with a 1 fs time step, and the SHAKE algorithm was used to constrain all bonds involving hydrogen atoms. Long-range electrostatics were handled by our IPS implementation with a cutoff of 10 Å. We also characterized temperature-dependent behavior by conducting simulations across a range of temperatures (240–380 K). Specific computational details and property calculation methodologies are consistent with our previous publications¹⁹ and are provided in the [Supporting Information](#).

For the alanine dipeptide, we focused on comparing the conformational free energy surfaces along the backbone dihedral angles ϕ and ψ . The comparison provides a sensitive test of how well DEGAUSS reproduces the conformational preferences of classical force fields, as even small deviations in the relative energies of different states can significantly alter the conformational equilibria. In our final validation tests, we examined the structural stability of well-characterized small proteins in solution, including 1PGA (protein G B1 domain), 1UBQ (ubiquitin), and 1ENH (engrailed homeodomain). For these proteins, we performed 10 replicas of 10 ns production runs after equilibration and analyzed the stability of the simulation by measuring RMSD from the X-ray crystallography structures.

Alchemical Free Energy Calculation. To demonstrate the capability of DEGAUSS for alchemical free energy calculations, we computed the hydration free energy of the Na^+ ion in water. The decoupling process was divided into two sequential stages: electrostatic and van der Waals contributions. For both DEGAUSS and classical force fields, we employed identical sampling protocols to ensure direct comparability: 11 equally spaced λ windows for electrostatic decoupling and 11 exponentially spaced windows for van der Waals decoupling. Each simulation window was run for 3 ns, with the first 1 ns discarded as equilibration and the subsequent 2 ns used for production and analysis. To verify the convergence and reliability of our alchemical calculations, we performed both forward (coupling to decoupling) and backward (decoupling to coupling) process sampling and confirmed that the free energy differences were consistent within statistical error, indicating proper equilibration and absence of hysteresis.

For the van der Waals decoupling stage, we employed exponentially spaced λ to ensure adequate sampling in regions with steep free energy gradients

$$\lambda_i = \frac{\exp(-((1 - i/n)a)^2) - \exp(-a^2)}{1 - \exp(-a^2)} \quad (18)$$

where $n = 10$ (for 11 windows), i ranges from 0 to n , and the control parameter a was set to 3. This exponential spacing concentrates sampling near the fully decoupled ($\lambda = 0$) and fully coupled ($\lambda = 1$) end points, where free energy gradients are largest.

For DEGAUSS, we employed the Bennett acceptance ratio (BAR) method to estimate free energy differences between adjacent λ states

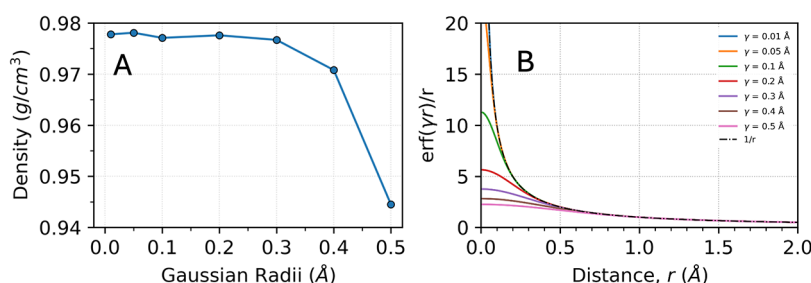


Figure 1. Characterization of Gaussian charge distribution effects using radius values of 0.01, 0.05, 0.1, 0.2, 0.3, 0.4, and 0.5 Å. (A) Water density as a function of Gaussian radius, showing stability for radius values below 0.3 Å and a significant drop as the radius increases to 0.5 Å. (B) Comparison of Gaussian electrostatic potentials with the classical Coulomb potential ($1/r$), demonstrating how the 0.2 Å radius closely approximates classical behavior above 0.5 Å while maintaining finite values at shorter distances.

$$\Delta G_{i \rightarrow i+1} = k_B T \ln \frac{\langle f(U_{i+1} - U_i + C) \rangle_i}{\langle f(U_i - U_{i+1} - C) \rangle_{i+1}} + C \quad (19)$$

where $f(x) = (1 + \exp(\beta x))^{-1}$ is the Fermi function, U_i is the potential energy at state i , $\langle \dots \rangle_i$ denotes the ensemble average at state i , and C is determined self-consistently. The alchemical transformation was implemented by manually adjusting the parameter topology file to gradually scale the atomic charges and decouple the van der Waals interactions through the scaling of the epsilon parameter. To obtain the potential energies required for BAR, a single-step energy minimization was performed on each frame from the simulation trajectory using topology parameters from neighboring λ windows.

For classical force fields, the direct perturbation approach used for DEGAUSS cannot be applied due to singularities in the Lennard-Jones potential that cause divergences near complete particle annihilation. Instead, we performed thermodynamic integration (TI) with the same 11-window protocol for each stage

$$\Delta G = \int_0^1 \left\langle \frac{\partial U(\lambda)}{\partial \lambda} \right\rangle_\lambda d\lambda \quad (20)$$

where λ is the coupling parameter and $\langle \dots \rangle_\lambda$ denotes the ensemble average at coupling parameter λ . For the van der Waals component, we used a softcore potential to avoid singularities

$$V_{\text{softcore}} = 4\epsilon(1 - \lambda) \left[\frac{1}{[\alpha\lambda + (r_{ij}/\sigma)^6]^2} - \frac{1}{\alpha\lambda + (r_{ij}/\sigma)^6} \right] \quad (21)$$

where α is the softcore parameter (set to 0.5), λ is the coupling parameter, and r_{ij} is the interatomic distance.

Code and Data Availability. The DEGAUSS implementation is currently available as a development branch of the PMEMD module and SANDER module in AMBER.⁴⁵ This modified codebase will be integrated into the official AMBER release in the next major release. Our implementation maintains the efficiency of the original code while adding the new potential functions and their IPS formulations. All simulation input files, parameters, and output data generated in this study are freely available in our GitHub repository (<https://github.com/larryhuang98/DEGAUSS-validation>). The benchmark simulations utilized classical force fields, including TIP3P and OPC3 for water models and FF19SB for proteins, all of which are publicly accessible through the AMBER software package.

RESULTS AND DISCUSSION

Optimization of DEGAUSS Parameters. *Characterization of Double Exponential Function van der Waals Potential.* We systematically investigated the parameters of the DE potential to determine the optimal values that can accurately reproduce the properties of the LJ potential. Our previous work²⁴ established the initial parameters ($\alpha = 17.470$, $\beta = 4.099$) by fitting to the TIP3P oxygen–oxygen LJ potential over the range between $r = 0.9r_m$ and $r = 5.0r_m$. While those parameters were able to reproduce the energy profile, when we tested further on bulk liquid water, the density was too low (the original double exponential parameters led to a density of 0.977 g/cm³). This is because in the immediate shorter region of the fitting range, DE is actually larger than LJ, which makes DE more repulsive than LJ. After enlarging the fitting range to include all accessible regions, the DE potential is similarly repulsive as the LJ. In particular, it is well-known that the first layer oxygen–oxygen distance of water peaks at around 2.8 Å,⁴⁶ notably shorter than the $r_m = 3.5$ Å in the TIP3P model, primarily due to strong H₂O...OH[−] hydrogen bonds. Therefore, an accurate interaction potential in the short range (approximately 2.8 Å) is needed. To reproduce water density, we refit over a shorter range from $r = 0.7r_m$ to $r = 3.0r_m$ and obtained $\alpha = 18.17$ and $\beta = 3.65$.

Effects of Gaussian Charge Distribution Radius. In addition to the parameters α and β that define the DE potential, a key parameter in the DEGAUSS model is the Gaussian radius, $1/\gamma$, which determines the spatial extent of the charge distributions. Computationally, $1/\gamma$ sets the threshold distance below which attenuation of the charge–charge interaction becomes significant. We initially explored a uniform model in which all atoms share the same Gaussian radius. Figure 1A illustrates the effect of varying the radius from 0.01 Å to 0.5 Å on the density of DEGAUSS water, which was parametrized to reproduce TIP3P, with the DE parameters fixed at their optimal values.

The results demonstrate that water density remains relatively stable for a radius below 0.3 Å, maintaining approximately 0.977 g/cm³. Beyond 0.3 Å, the density begins to decrease noticeably, dropping to about 0.945 g/cm³ at 0.5 Å. This behavior reflects that the electrostatic interactions in water are predominantly long-range in nature, and the DE potential prevents the oxygen–oxygen distances from falling too close to each other, where charge overlap becomes significant. Figure 1B compares the Gaussian electrostatic potential for various radii $1/\gamma$ with the classical Coulombic $1/r$ potential. For a radius of $1/\gamma = 0.2$ Å, the Gaussian potential closely matches the Coulomb potential down to distances as close as 0.5 Å,

deviating from this only at shorter ranges. In comparison, the shortest experimentally observed oxygen–oxygen distances are about 2.4 Å⁴⁶ at or near room temperature. Thus, under typical biomolecular simulation conditions, usually conducted at or near room temperature, oxygen–oxygen distances are highly unlikely to fall below 0.5 Å, where deviations between the Gaussian and Coulomb potentials would become significant. Therefore, we chose $1/\gamma = 0.2$ Å for the DEGAUSS model that is well justified for modeling electrostatics in such simulations. This value provides an optimal balance between maintaining accurate electrostatic potential at typical interaction distances while ensuring finite energies when atoms become close to each other, effectively eliminating electrostatic singularities without significantly perturbing the system's physical properties.

Validation of DEGAUSS with TIP3P Water System.

After establishing the optimal parameters for the DEGAUSS model, we conducted comprehensive validation against the reference TIP3P water model. Our assessment focused on both thermodynamic properties under ambient conditions and temperature-dependent behavior.

Table 1 compares the key thermodynamic properties between the TIP3P and TIP3P-DEGAUSS models at 298 K

Table 1. Model Bulk Properties of Water at Ambient Conditions (298 K, 1 bar): Dipole Moment μ , Density ρ , Static Dielectric Constant ϵ_0 , Self-Diffusion Coefficient D , Heat of Vaporization ΔH_{vap} , First Peak Position in the RDF r_{OOL} , Isobaric Heat Capacity C_p , Thermal Expansion Coefficient α_p , and Isothermal Compressibility κ_T

property	experimental ^{47–50}	TIP3P	TIP3P-DEGAUSS
ρ [g/cm ³]	0.997	0.984 ± 0.002	0.984 ± 0.002
ϵ_0	78.4	106.5 ± 3.8	101.6 ± 1.2
D [10 ⁹ m ² /s]	2.30	6.29 ± 0.18	5.72 ± 0.31
ΔH_{vap} [kcal/mol]	10.52	10.38 ± 0.001	10.18 ± 0.002
r_{OOL} [Å]	2.85	2.77 ± 0.003	2.78 ± 0.007
C_p [cal/(K·mol)]	18.0	14.0 ± 0.1	14.0 ± 0.8
α_p [10 ^{−4} K ^{−1}]	2.57	9.08 ± 0.05	8.90 ± 0.05
κ_T [10 ^{−6} bar ^{−1}]	45.9	58.8 ± 1.7	58.4 ± 2.0

and 1 bar. The DEGAUSS model successfully reproduces most properties of TIP3P water with excellent accuracy, maintaining nearly identical density (0.984 g/cm³ vs 0.984 g/cm³) and similar first peak position in the radial distribution function (2.78 vs 2.77 Å). Several properties show notable improvements over TIP3P: the self-diffusion coefficient decreases significantly (5.72 vs 6.29 × 10⁹ m²/s), approaching the experimental value of 2.30 × 10⁹ m²/s. The static dielectric constant (101.6 vs 106.5) moves closer to the experimental value of 78.4. The heat capacity shows consistent result (14.0 vs 14.0 cal/(K·mol)).

We further examined the temperature dependence of water density from 240 to 380 K (Figure 2). The DEGAUSS and TIP3P models exhibit nearly identical behavior throughout the entire temperature range, with the curves virtually overlapping. This excellent agreement demonstrates that the DEGAUSS model maintains the essential temperature-dependent properties of TIP3P while preserving its thermodynamic consistency. This consistency extends to the isothermal compressibility, where both models show nearly identical slopes at 298 K.

These results confirm that the DEGAUSS model accurately reproduces the essential thermodynamic properties of the TIP3P water model while offering improvements in several key areas. The softcore nature of the potentials appears to have beneficial effects on the dynamic properties and dielectric behavior, bringing the model closer to experimental observations without compromising the structural integrity of the original TIP3P framework.

Validation of DEGAUSS with OPC3 Water Model.

While the TIP3P water model is widely used in biomolecular simulations, it has known limitations in reproducing certain experimental properties, particularly the temperature of maximum density (TMD) and dielectric constant. To address these limitations, we implemented the DEGAUSS approach for the OPC3 water model, which offers improved accuracy for many thermodynamic and structural properties of water.

The OPC3-DEGAUSS model used the same double exponential α and β values as with TIP3P. Table 2 compares the properties of the original OPC3 model with our implementation of the OPC3-DEGAUSS under ambient conditions.

The OPC3-DEGAUSS model successfully reproduces the density of OPC3 water (0.995 g/cm³ vs 0.995 g/cm³) and maintains the improved structural and thermodynamic properties that make OPC3 superior to TIP3P for many applications. The dielectric constant increases from 78.4 to 80.38. Self-diffusion decreases slightly from 2.92 to 2.62 × 10⁹ m²/s, moving closer to the experimental value of 2.30 × 10⁹ m²/s. The heat of vaporization increases modestly (12.35 vs 12.32 kcal/mol).

Figure 3 illustrates the temperature dependence of water density for both OPC3 and OPC3-DEGAUSS from 240 to 380 K. Both models exhibit the characteristic density maximum around the TMD, with the curves virtually overlapping throughout the entire temperature range. This excellent agreement extends to the TMD and isothermal compressibility, which remain almost identical for both models.

These results demonstrate that the DEGAUSS approach can be successfully applied to more sophisticated water models like the OPC3, maintaining or even enhancing their thermodynamic and structural properties while providing the computational advantages of continuous potentials. The robust transferability of our parametrization strategy across different water models suggests that DEGAUSS can be effectively implemented with other force fields to support a wide range of molecular simulation applications.

Validation of DEGAUSS with Alanine Dipeptide.

Beyond water models, we evaluated the DEGAUSS force field using the alanine dipeptide, a prototypical system for proteins. This small peptide serves as an ideal test case due to its well-characterized conformational landscape and combination of backbone and side chain interactions, providing insights into how the singularity-free DEGAUSS potentials affect protein conformational preferences.

We investigated the free energy surface of the alanine dipeptide in explicit water through 100 ns simulations (Figure 4). The Ramachandran-style free energy landscapes for both DEGAUSS and classical force fields show remarkable similarity. Both force fields correctly identify the major free energy minima corresponding to the characteristic conformational regions: the PPII region ($\Phi \approx -75^\circ$, $\Psi \approx 150^\circ$), the α_R region ($\Phi \approx -75^\circ$, $\Psi \approx -40^\circ$), and the β region ($\Phi \approx -150^\circ$, $\Psi \approx 150^\circ$). The free energy basins exhibit nearly identical

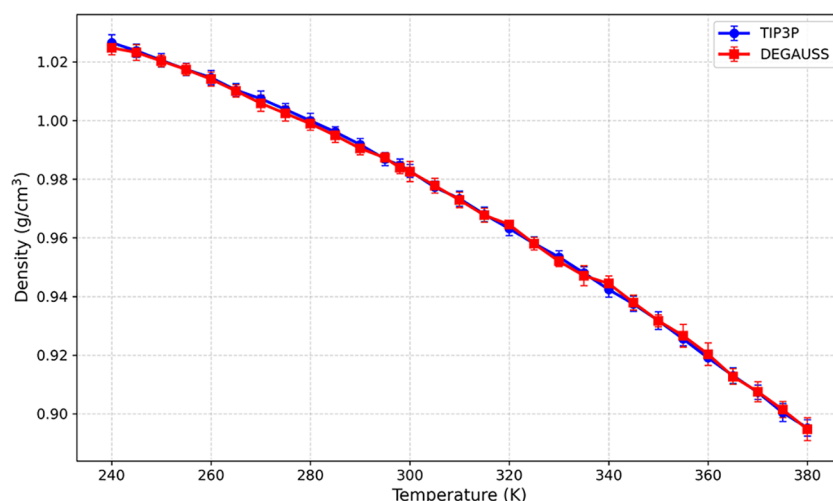


Figure 2. Temperature dependence of water density for TIP3P (blue circles) and DEGAUSS (red squares) models from 240 to 380 K at 1 bar pressure. Error bars represent standard errors estimated using block averaging. The DEGAUSS model closely follows the TIP3P behavior across the entire temperature range.

Table 2. Model Bulk Properties of Water at Ambient Conditions (298 K, 1 bar): Dipole Moment μ , Density ρ , Static Dielectric Constant ϵ_0 , Self-Diffusion Coefficient D , Heat of Vaporization ΔH_{vap} , First Peak Position in the RDF r_{Oo1} , Isobaric Heat Capacity C_p , Thermal Expansion Coefficient α_p , and Isothermal Compressibility κ_T

property	experimental ^{147–50}	OPC3	OPC3-DEGAUSS
ρ [g/cm ³]	0.997	0.995 $\pm$ 0.001	0.995 $\pm$ 0.001
ϵ_0	78.4	78.40 $\pm$ 1.76	80.38 $\pm$ 3.00
D [10^9 m ² /s]	2.30	2.92 $\pm$ 0.17	2.62 $\pm$ 0.19
ΔH_{vap} [kcal/mol]	10.52	12.32 $\pm$ 0.004	12.35 $\pm$ 0.003
r_{Oo1} [Å]	2.85	2.76 $\pm$ 0.003	2.76 $\pm$ 0.002
C_p [cal/(K·mol)]	18.0	14.5 $\pm$ 0.2	15.1 $\pm$ 0.2
α_p [10^{-4} K ⁻¹]	2.57	4.54 $\pm$ 0.08	4.40 $\pm$ 0.05
κ_T [10^{-6} bar ⁻¹]	45.9	43.11 $\pm$ 0.31	42.95 $\pm$ 0.84
TMD [K]	277	246.6 $\pm$ 1.8	248.5 $\pm$ 0.9

locations and depths between the two force fields with both showing the characteristic diagonal pattern of accessible conformational space. The differences between the two force fields are very small, indicating excellent agreement in the conformational sampling.

To further validate the similarity, we analyzed the Φ dihedral angle distribution (Figure S3 in the Supporting Information). The Φ distribution from DEGAUSS closely matches that from FF19SBTIP3P, with the probability densities overlapping across all major conformational states, further confirming that DEGAUSS can successfully recover the classical force field properties.

These results demonstrate that DEGAUSS can effectively reproduce the conformational properties of classical force fields without extensive reparameterization. The dominant conformational states are well-preserved with nearly identical free energy values, making DEGAUSS a practical alternative to classical force fields for peptide and protein simulations. The smooth, continuous nature of the potentials offers particular

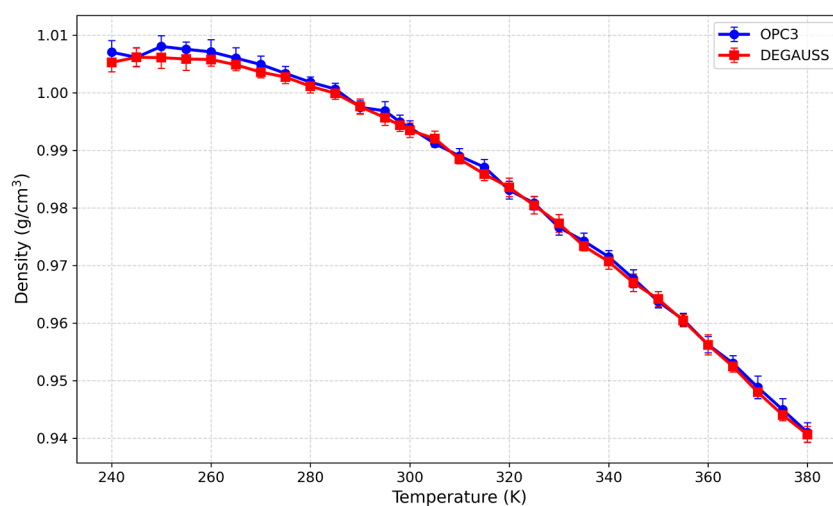


Figure 3. Temperature dependence of water density for OPC3 (blue circles) and OPC3-DEGAUSS (red squares) models from 240 to 380 K at 1 bar pressure. Error bars represent standard errors estimated using block averaging. Both models exhibit nearly identical density–temperature behavior.

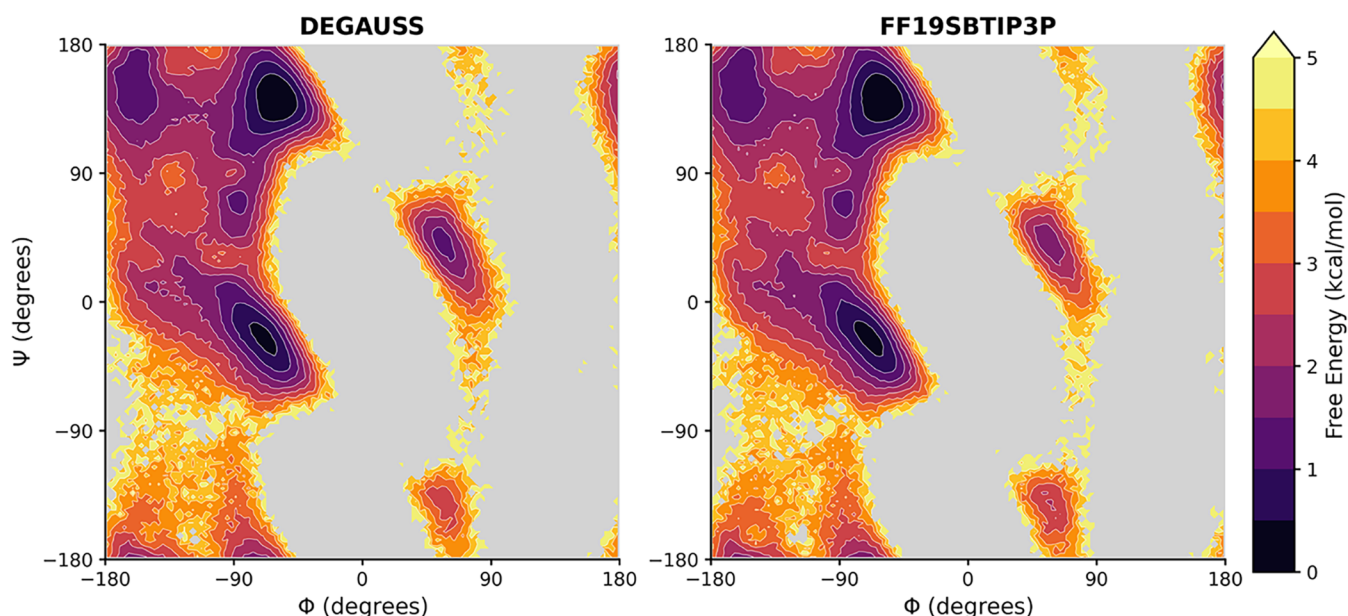


Figure 4. Free energy surfaces of the alanine dipeptide in explicit water obtained from 100 ns simulations comparing DEGAUSS (left) and FF19SBTIP3P (right) force fields. The landscapes show the relative free energies (kcal/mol) as a function of the Φ and Ψ backbone dihedral angles. Both force fields reproduce the characteristic conformational regions: PPII ($\Phi \approx -75^\circ$, $\Psi \approx 150^\circ$), α_R ($\Phi \approx -75^\circ$, $\Psi \approx -40^\circ$), and β ($\Phi \approx -150^\circ$, $\Psi \approx 150^\circ$) states, with remarkable agreement in basin locations and relative energies.

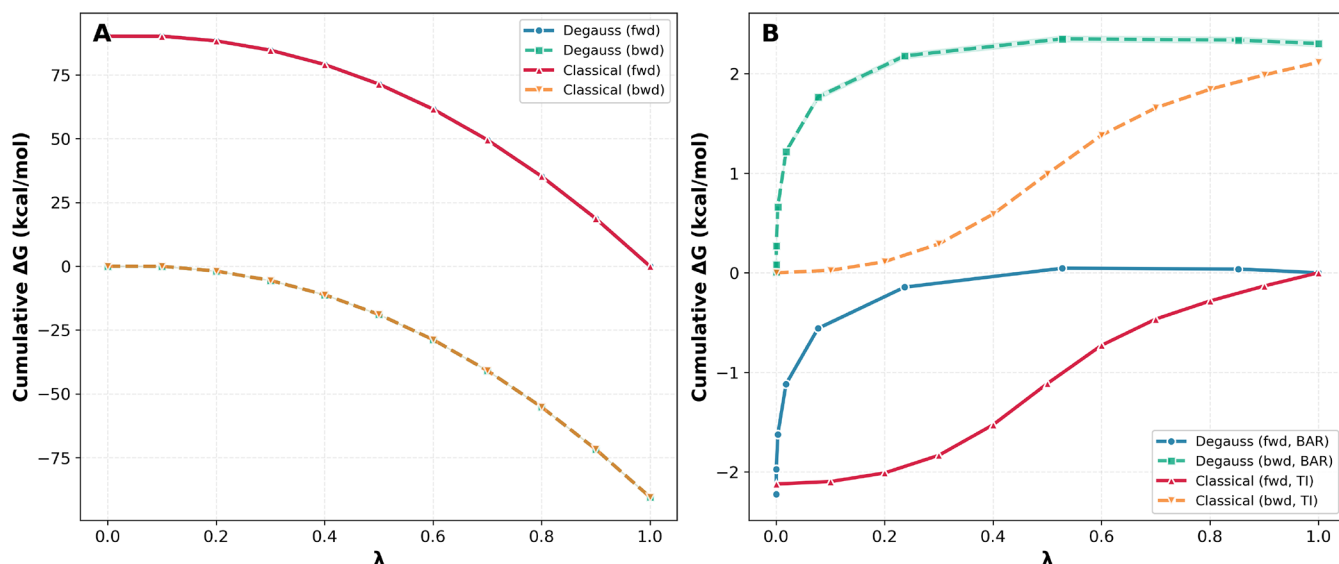


Figure 5. Hydration free energy calculations for the Na^+ ion comparing DEGAUSS and classical force fields. (A) Electrostatic contribution showing forward and backward free energy profiles as a function of λ , where $\lambda = 0$ represents the fully decoupled state and $\lambda = 1$ represents the fully coupled state. The curves for DEGAUSS and classical force fields are virtually overlapping, both using the isotropic periodic sum (IPS). (B) van der Waals contribution with DEGAUSS using direct decoupling and classical force field employing thermodynamic integration with softcore potentials. While the final free energies agree closely, the curves differ due to the distinct alchemical pathways employed by each method.

advantages for enhanced sampling methods and simulations involving conformational transitions, where the singularities in classical potentials can create numerical instabilities while maintaining the accuracy of classical force fields in describing equilibrium conformational distributions.

Validation of DEGAUSS with Small Proteins. To evaluate the performance of DEGAUSS on realistic biomolecular systems, we conducted simulations on three small proteins representing different structural classes: engrailed homeodomain (, α -helical), ubiquitin (, mixed α/β), and protein G (, predominantly β -sheet). All simulations were

performed as 10 independent replicas of 10 ns each, allowing for a statistical analysis of the results.

We assessed the force field's ability to maintain protein stability through multiple structural metrics (Figures S4–S7 in the Supporting Information). Secondary structure analysis using DSSP (Figure S4) shows that DEGAUSS reproduces the native secondary structure profiles nearly identical with FF19SB across all three proteins. The engrailed homeodomain maintains its characteristic three-helix bundle, ubiquitin preserves its complex α/β fold, and protein G retains its predominantly β -sheet architecture.

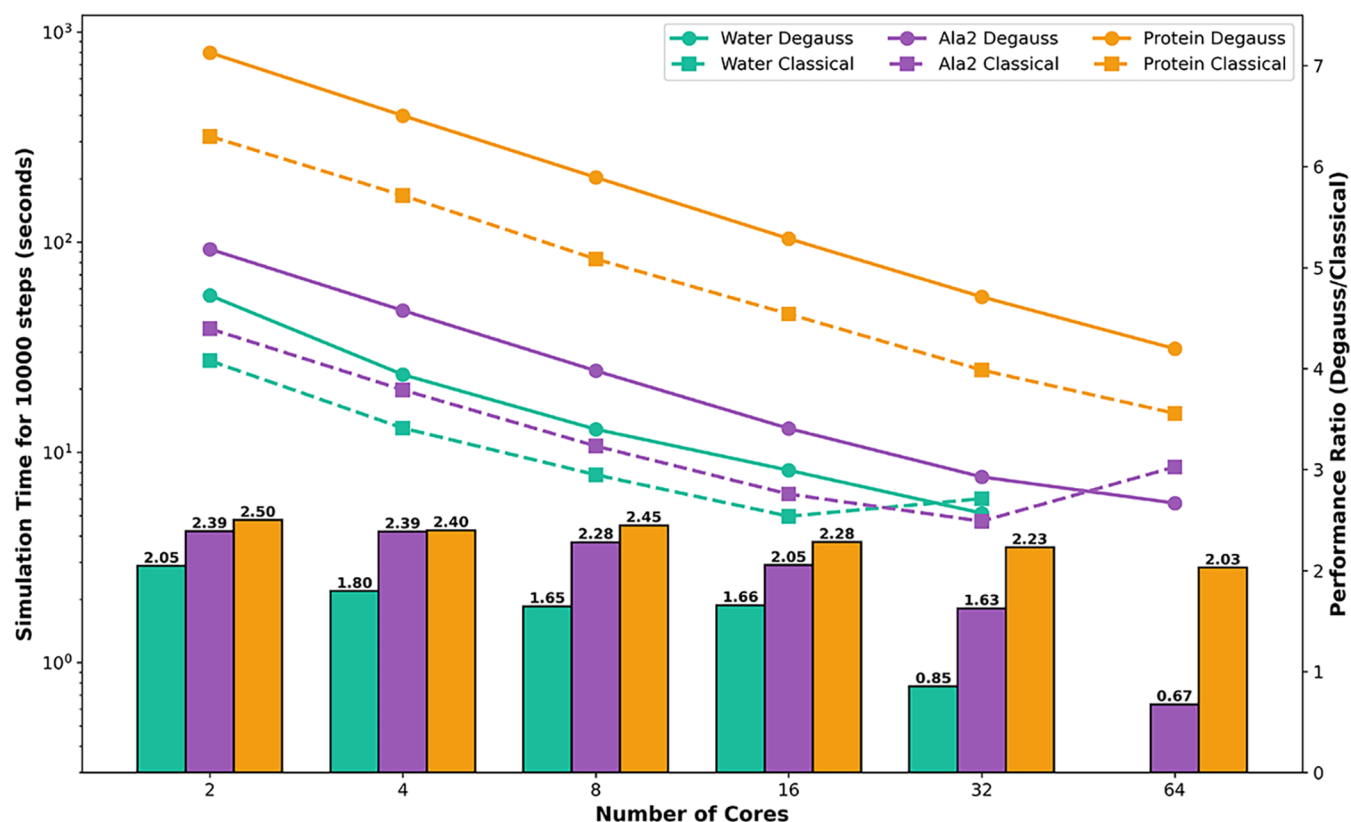


Figure 6. Performance comparison between DEGAUSS and classical force fields across three benchmark systems showing simulation times (lines) and performance ratios (bars). DEGAUSS is approximately 2 times slower but exhibits better parallel scaling at higher core counts.

Backbone RMSD analysis (Figure S5) reveals structural stability comparable to that between the two force fields. For engrailed homeodomain, a slight deviation appears at the end of the simulation but remains within 0.5 Å. For ubiquitin and protein G, the RMSD curves are virtually overlapping, indicating excellent structural maintenance. Per-residue RMSF profiles (Figure S6) exhibit consistent fluctuation patterns between DEGAUSS and FF19SB, with ubiquitin showing nearly identical values, while engrailed homeodomain and protein G display good agreement in capturing residue-level dynamics. The radii of gyration distributions (Figure S7) are also highly similar, with most data points overlapping and differences remaining under 0.5 Å even when individual simulations sample slightly different conformational states.

These results demonstrate that DEGAUSS preserves essential protein structural features while providing the computational advantages of continuous, singularity-free potentials. The consistent performance across different protein architectures validates the force field's applicability to diverse biomolecular systems. It is important to note that perfect reproduction of classical force field behavior is not expected as the current implementation directly borrows parameters from classical force fields. More rigorous comparisons will be possible once DEGAUSS undergoes a systematic reparameterization tailored to its singularity-free functional form.

Hydration Free Energy of Na⁺. To demonstrate a key advantage of the DEGAUSS force field, we computed the hydration free energy of Na⁺ and showed that DEGAUSS accurately reproduces classical force field alchemical calculation results without requiring additional softcore potential modifications. Although DEGAUSS is inherently singularity-

free, linear λ spacing would cause improper sampling of the repulsive core region. Therefore, it is necessary to employ the exponentially spaced windows.

To ensure rigorous and systematic comparison, we performed both forward (coupling-decoupling) and backward (decoupling-coupling) simulations to verify convergence and sampling adequacy. In our alchemical pathway, we define $\lambda = 0$ as the fully decoupled (disappeared) state and $\lambda = 1$ as the fully coupled (existing) state. Figure 5 presents the free energy profiles for both electrostatic (panel A) and van der Waals (panel B) contributions.

For the electrostatic contribution (Figure 5A), the free energy curves for DEGAUSS and classical force fields overlap throughout the entire λ range. DEGAUSS yields a forward free energy of $\Delta G_{\text{forward}} = 90.156 \pm 0.059$ kcal/mol and a backward free energy of $\Delta G_{\text{backward}} = -90.428 \pm 0.059$ kcal/mol, with a hysteresis of less than 0.3 kcal/mol, indicating excellent convergence. The classical force field shows virtually identical values: $\Delta G_{\text{forward}} = 90.157 \pm 0.059$ kcal/mol and $\Delta G_{\text{backward}} = -90.428 \pm 0.060$ kcal/mol. The agreement between DEGAUSS and classical force fields is remarkable with differences at the 0.001 kcal/mol level. Both calculations employed the isotropic periodic sum (IPS) method, as particle-mesh Ewald (PME) can introduce artifacts when decoupling unbalanced charge systems.

The van der Waals contribution (Figure 5B) shows similar agreement in the final free energy values, although the curves themselves differ due to the distinct alchemical pathways. DEGAUSS gives $\Delta G_{\text{forward}} = -2.226 \pm 0.029$ kcal/mol and $\Delta G_{\text{backward}} = 2.303 \pm 0.030$ kcal/mol. For the classical force field using thermodynamic integration with softcore potentials,

we obtain $\Delta G_{\text{forward}} = -2.122 \pm 0.073$ kcal/mol and $\Delta G_{\text{backward}} = 2.114 \pm 0.073$ kcal/mol. While the integrated free energies agree within 0.2 kcal/mol, the different functional forms, DEGAUSS's direct decoupling versus classical softcore potential, result in distinct curve shapes along the alchemical pathway, validating DEGAUSS's ability to reach the same thermodynamic end point through a different route.

A key insight from these results is that DEGAUSS reproduces free energies of classical force fields while avoiding the singularity problem. Unlike classical methods that require artificial softcore modifications to avoid singularities, DEGAUSS performs the transformation directly without shifting the potential energy surface. This demonstrates that the singularity-free formulation of DEGAUSS not only reproduces classical force field thermodynamics but also provides a more straightforward implementation for free energy calculations.

Performance. We conducted performance benchmarks on three representative systems: 512 water molecules, 620 water molecules with alanine dipeptide, and engailed homeodomain in NaCl solution (15,673 atoms total). Each system was simulated for 10,000 steps with three independent replicates. The DEGAUSS functional forms require one additional error function evaluation per electrostatic pairwise interaction and two additional exponential calculations per van der Waals interaction compared to classical force fields as well as some other computational overheads in IPS formulism.

As shown in Figure 6, the current unoptimized implementation of DEGAUSS is approximately 2-fold slower than classical force fields across all tested systems. However, DEGAUSS demonstrates superior multicore scaling compared to classical force fields with PME, with the performance gap narrowing significantly as the number of cores increases. While the current computational cost is higher, it remains acceptable for practical applications, and substantial performance improvements are expected through future code optimization.

About van der Waals Potential Parameterization. In molecular mechanics force fields, the nonbonded interactions are often treated by a combination of electrostatic and van der Waals terms. While the electrostatic terms are obtained from ab initio quantum mechanical calculations, the van der Waals parameters are usually obtained empirically by fitting experimental data. Shown in Figure S1 are comparisons of the three representative sets. In the DblExp1 set, $\alpha = 17.470$ and $\beta = 4.099$ were obtained by fitting to the LJ potential in the range of $r = 0.9r_m$ to $r = 5.0r_m$. Here, for the TIP3P model, the $r_m = 3.5$ Å. Therefore, $r = 0.9r_m$ and $r = 5.0r_m$ correspond to 3.2 and 17.7 Å, respectively. Because the first layer oxygen–oxygen distance is approximately 2.8 Å, the range from 3.2 to 17.7 Å is obviously beyond the first layer, which results in a more repulsive DE energy near the lower boundary of the fitting range, here, 3.2 Å. In essence, this approach neglects the most critical energetic region in parametrization. It is therefore not surprising that when the LJ potentials were substituted by the DE function with DblExp1 parameters, the densities of both TIP3P-DEGAUSS and the OPC-DEGAUSS models deviated notably away from the LJ densities (Figure S2). In comparison, the DblExp2 set with parameters $\alpha = 18.17$ and $\beta = 3.65$ resulted in models that essentially matched those using LJ potentials, in terms of liquid densities (Figures 2 and 3).

Importantly, the energy curves are very close to each other. Figure S1 clearly illustrates that all three double exponential van der Waals functions can reproduce the Lennard-Jones 6–12 potential well, particularly and not surprisingly in the region

around $r = r_m$. In the region close to the first layer oxygen–oxygen distance of about 2.8 Å, the differences are smaller than 0.05 kcal/mol. Yet, even such a tiny energy difference resulted in notably different liquid behavior. Such an exquisite level of accuracy is still a challenge to obtain even for modern computational resources, particularly if we consider the need to perform such calculations in a liquid-like environment (e.g., large clusters). Hence, we envision that fitting to experimental data will likely remain the method of choice for some time.

CONCLUSION

We have successfully demonstrated that the DEGAUSS force field can accurately reproduce the behavior of classical force fields while eliminating their inherent mathematical singularities. Our comprehensive validation across multiple molecular systems confirms that DEGAUSS can maintain physical accuracy without the limitations that typically plague alchemical simulations.

The systematic parameter optimization revealed that DE potentials combined with Gaussian charge distributions can faithfully reproduce classical force field behaviors, requiring minimal adjustments to restore accurate thermodynamic properties while preserving the advantages of singularity-free potentials.

For water systems, DEGAUSS successfully reproduced key properties of both TIP3P and OPC3 models, maintaining density, dielectric constant, and temperature dependence nearly identical to those of the original models. Several properties showed improvements. The temperature of the maximum density for the OPC3 water also improved, approaching the experimental value.

Biomolecular validation revealed that DEGAUSS preserves the essential features of protein conformational landscapes. Alanine dipeptide simulations showed that major conformational states are correctly identified, though with slightly restricted sampling of less favorable conformations. This behavior reflects the inherent nature of the DEGAUSS interactions, which tend to stabilize low-energy conformations while creating higher barriers for unfavorable transitions.

Protein simulations demonstrated excellent structural stability across a variety of fold types. All three test proteins, the all- α engrailed homeodomain, the predominantly β protein G B1 domain, and the mixed α/β ubiquitin, maintained their native conformations with backbone RMSD values comparable to classical force field simulations. Backbone fluctuation patterns correctly identified flexible regions while preserving the secondary structure integrity. This consistent performance across α -helical, β -sheet, and mixed α/β topologies confirms that DEGAUSS captures the essential balance of interactions required for protein stability without introducing artificial flexibility or compromising structural integrity.

Our alchemical free energy calculation results support our key findings. With the same parameters from its corresponding classical force field, DEGAUSS produces the alchemical free energies highly consistent with those in the classical force field for both electrostatic contributions and van der Waals contributions. Importantly, DEGAUSS achieves this without requiring additional softcore potentials, constructing an alchemical pathway where the potential energy surface remains minimally perturbed.

Future developments will focus on two primary directions. First, we will explore the performance of DEGAUSS in alchemical free energy calculations, showcasing its advantages

over traditional softcore approaches for both small molecule solvation and protein–ligand binding free energies. Second, we will explore the development of water models specifically parametrized for DEGAUSS, taking advantage of the unique properties of three-point rigid water models within our theoretical framework. Such models have the potential to achieve improved accuracy by leveraging the inherent capabilities of DEGAUSS rather than simply reproducing existing force field behaviors.

These results establish DEGAUSS as a viable alternative to classical force fields that maintain accuracy while providing the mathematical advantages needed for challenging simulation applications. The successful validation across diverse molecular systems demonstrates the broad applicability of this approach for advancing molecular simulation methodology.

■ ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.jctc.5c01324>.

Section S1 shows the simulation details for each part of the simulation. Figure S1 shows the comparison between different double exponential models. Figure S2 shows the temperature-density behavior of different exponential coefficients. Figure S3 shows the Φ dihedral angle distribution of alanine dipeptide. Figure S4 shows the secondary structure profiles for the three tested proteins. Figure S5 shows the backbone RMSD time series. Figure S7 shows the per-residue RMSF profiles. Figure S7 shows the radius of gyration distributions. Figures S8–S12 show the convergence and detailed analysis for the DEGAUSS-TIP3P water system, including total energy (Figure S8), density (Figure S9), dielectric constant (Figure S10), radial distribution functions (Figure S11), and the velocity autocorrelation function (Figure S12) (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Xiongwu Wu – Laboratory of Computational Biology, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland 20892, United States; Email: wuxw@nhlbi.nih.gov

Ray Luo – Chemical, Applied, and Materials Physics Graduate Program, Departments of Molecular Biology and Biochemistry, Chemical and Biomolecular Engineering, Materials Science and Engineering, and Biomedical Engineering, University of California, Irvine, California 92697, United States; orcid.org/0000-0002-6346-8271; Email: rluo@uci.edu

Authors

Zhen Huang – Chemical, Applied, and Materials Physics Graduate Program, Departments of Molecular Biology and Biochemistry, Chemical and Biomolecular Engineering, Materials Science and Engineering, and Biomedical Engineering, University of California, Irvine, California 92697, United States; orcid.org/0009-0003-4478-8477

Yong Duan – Genome Center, University of California, Davis, California 95616, United States; Department of Biomedical Engineering, University of California, Davis, California 95616, United States; orcid.org/0000-0003-3793-5099

Complete contact information is available at:

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Notes

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■ REFERENCES

- (1) Karplus, M.; McCammon, J. A. Molecular dynamics simulations of biomolecules. *Nat. Struct. Biol.* **2002**, *9*, 646–652.
- (2) MacKerell, A. D., Jr Empirical force fields for biological macromolecules: overview and issues. *J. Comput. Chem.* **2004**, *25*, 1584–1604.
- (3) Vanommeslaeghe, K.; Hatcher, E.; Acharya, C.; Kundu, S.; Zhong, S.; Shim, J.; Darian, E.; Guvench, O.; Lopes, P.; Vorobyov, I.; Mackerell, A. D. CHARMM general force field: A force field for drug-like molecules compatible with the CHARMM all-atom additive biological force fields. *J. Comput. Chem.* **2010**, *31*, 671–690.
- (4) Wang, J.; Wolf, R. M.; Caldwell, J. W.; Kollman, P. A.; Case, D. A. Development and testing of a general amber force field. *J. Comput. Chem.* **2004**, *25*, 1157–1174.
- (5) Cornell, W. D.; Cieplak, P.; Bayly, C. I.; Gould, I. R.; Merz, K. M.; Ferguson, D. M.; Spellmeyer, D. C.; Fox, T.; Caldwell, J. W.; Kollman, P. A. A second generation force field for the simulation of proteins, nucleic acids, and organic molecules. *J. Am. Chem. Soc.* **1995**, *117*, S179–S197.
- (6) Ponder, J. W.; Case, D. A. Force fields for protein simulations. *Adv. Protein Chem.* **2003**, *66*, 27–85.
- (7) Schwerdtfeger, P.; Wales, D. J. 100 years of the Lennard-Jones potential. *J. Chem. Theory Comput.* **2024**, *20*, 3379–3405.
- (8) Buckingham, R. A. The classical equation of state of gaseous helium, neon and argon. *Proc. R. Society London Series A. Mathemat. Phys. Sci.* **1938**, *168*, 264–283.
- (9) Halgren, T. A. The representation of van der Waals (vdW) interactions in molecular mechanics force fields: potential form, combination rules, and vdW parameters. *J. Am. Chem. Soc.* **1992**, *114*, 7827–7843.
- (10) Ponder, J. W.; Wu, C.; Ren, P.; Pande, V. S.; Chodera, J. D.; Schnieders, M. J.; Haque, I.; Mobley, D. L.; Lambrecht, D. S.; DiStasio, R. A., Jr; et al. Current status of the AMOEBA polarizable force field. *J. Phys. Chem. B* **2010**, *114*, 2549–2564.
- (11) Lamoureux, G.; MacKerell, A., Jr; Roux, B. A simple polarizable model of water based on classical Drude oscillators. *J. Chem. Phys.* **2003**, *119*, S185–S197.
- (12) Yu, H.; Hansson, T.; van Gunsteren, W. Development of a simple, self-consistent polarizable model for liquid water. *J. Chem. Phys.* **2003**, *118*, 221–234.
- (13) Ren, P.; Ponder, J. Polarizable atomic multipole water model for molecular mechanics simulation. *J. Phys. Chem. B* **2003**, *107*, S933–S947.
- (14) Burnham, C. J.; Li, J.; Xantheas, S.; Leslie, M. The parametrization of a Thole-type all-atom polarizable water model from first principles and its application to the study of water clusters ($n = 2–21$) and the phonon spectrum of ice Ih. *J. Chem. Phys.* **1999**, *110*, 4566–4581.
- (15) Caldwell, J.; Dang, L.; Kollman, P. Implementation of nonadditive intermolecular potentials by use of molecular dynamics: development of a water-water potential and water-ion cluster interactions. *J. Am. Chem. Soc.* **1990**, *112*, 9144–9147.
- (16) Wang, J.; Cieplak, P.; Li, J.; Wang, J.; Cai, Q.; Hsieh, M.; Lei, H.; Luo, R.; Duan, Y. Development of Polarizable Models for Molecular Mechanical Calculations II: Induced Dipole Models Significantly Improve Accuracy of Intermolecular Interaction Energies. *J. Phys. Chem. B* **2011**, *115*, 3100–3111.

- (17) Wei, H.; Qi, R.; Wang, J.; Cieplak, P.; Duan, Y.; Luo, R. Efficient formulation of polarizable Gaussian multipole electrostatics for biomolecular simulations *J. Chem. Phys.* 2020; Vol. 153, DOI: 10.1063/5.0019560.
- (18) Elking, D.; Darden, T.; Woods, R. J. Gaussian induced dipole polarization model. *J. Comput. Chem.* 2007, 28, 1261–1274.
- (19) Huang, Z.; Wu, Y.; Duan, Y.; Luo, R. Performance Tuning of Polarizable Gaussian Multipole Model in Molecular Dynamics Simulations. *J. Chem. Theory Comput.* 2025, 21, 847 DOI: 10.1021/acs.jctc.4c01368.
- (20) Huang, Z.; Zhao, S.; Cieplak, P.; Duan, Y.; Luo, R.; Wei, H. Optimal Scheme to Achieve Energy Conservation in Induced Dipole Models. *J. Chem. Theory Comput.* 2023, 19, 5047–5057.
- (21) Rick, S. W.; Stuart, S.; Berne, B. Dynamical fluctuating charge force fields: Application to liquid water. *J. Chem. Phys.* 1994, 101, 6141–6156.
- (22) York, D. M. Modern alchemical free energy methods for drug discovery explained. *ACS Phys. Chem. Au* 2023, 3, 478–491.
- (23) Tsai, H.-C.; Lee, T.-S.; Ganguly, A.; Giese, T. J.; Ebert, M. C.; Labute, P.; Merz, K. M., Jr; York, D. M. AMBER free energy tools: a new framework for the design of optimized alchemical transformation pathways. *J. Chem. Theory Comput.* 2023, 19, 640–658.
- (24) Wu, X.; Brooks, B. R. A double exponential potential for van der Waals interaction. *AIP Adv.* 2019, 9, No. 065304.
- (25) Man, V. H.; Wu, X.; He, X.; Xie, X.-Q.; Brooks, B. R.; Wang, J. Determination of van der Waals parameters using a double exponential potential for nonbonded divalent metal cations in TIP3P solvent. *J. Chem. Theory Comput.* 2021, 17, 1086–1097.
- (26) Duan, Y.; Niu, T.; Wang, J.; Cieplak, P.; Luo, R. PCMRSP: AMethod for Polarizable Force Field Parameter Development and Transferability of the Polarizable Gaussian Multipole Models Across Multiple Solvents. *J. Chem. Theory Comput.* 2024, 20, 2820–2829.
- (27) Duan, Y.; Wang, J.; Cieplak, P.; Luo, R. Refinement of Atomic Polarizabilities for a Polarizable Gaussian Multipole Force Field with Simultaneous Considerations of Both Molecular Polarizability Tensors and In-Solution Electrostatic Potentials. *J. Chem. Inf. Model.* 2025, 65, 1428–1440.
- (28) Zhao, S.; Cieplak, P.; Duan, Y.; Luo, R. Transferability of the Electrostatic Parameters of the Polarizable Gaussian Multipole Model. *J. Chem. Theory Comput.* 2023, 19, 924–941.
- (29) Zhao, S.; Cieplak, P.; Duan, Y.; Luo, R. Assessment of Amino Acid Electrostatic Parametrizations of the Polarizable Gaussian Multipole Model. *J. Chem. Theory Comput.* 2024, 20, 2098–2110.
- (30) Zhao, S.; Wei, H.; Cieplak, P.; Duan, Y.; Luo, R. PyRESP: A Program for Electrostatic Parameterizations of Additive and Induced Dipole Polarizable Force Fields. *J. Chem. Theory Comput.* 2022, 18, 3654–3670.
- (31) Zhao, S.; Wei, H.; Cieplak, P.; Duan, Y.; Luo, R. Accurate Reproduction of Quantum Mechanical Many-Body Interactions in Peptide Main-Chain Hydrogen-Bonding Oligomers by the Polarizable Gaussian Multipole Model. *J. Chem. Theory Comput.* 2022, 18, 6172–6188.
- (32) Zhu, Q.; Wu, Y.; Zhao, S.; Cieplak, P.; Duan, Y.; Luo, R. Streamlining and Optimizing Strategies of Electrostatic Parameterization. *J. Chem. Theory Comput.* 2023, 19, 6353–6365.
- (33) Wu, X.; Brooks, B. Isotropic periodic sum: a method for the calculation of long-range interactions. *J. Chem. Phys.* 2005, 122, No. 44107.
- (34) Wu, X.; Brooks, B. Using the isotropic periodic sum method to calculate long-range interactions of heterogeneous systems. *J. Chem. Phys.* 2008, 129, No. 154115.
- (35) Wu, X.; Brooks, B. Isotropic periodic sum of electrostatic interactions for polar systems. *J. Chem. Phys.* 2009, 131, No. 024107.
- (36) Wu, X.; Pickard, F. I.; Brooks, B. Isotropic periodic sum for multipole interactions and a vector relation for calculation of the Cartesian multipole tensor. *J. Chem. Phys.* 2016, 145, No. 164110.
- (37) Wu, X.; Brooks, B. The homogeneity condition: A simple way to derive isotropic periodic sum potentials for efficient calculation of long-range interactions in molecular simulation. *J. Chem. Phys.* 2019, 150, No. 214109.
- (38) Jorgensen, W. L.; Chandrasekhar, J.; Madura, J. D.; Impey, R. W.; Klein, M. L. Comparison of simple potential functions for simulating liquid water. *J. Chem. Phys.* 1983, 79, 926–935.
- (39) Izadi, S.; Onufriev, A. V. Accuracy limit of rigid 3-point water models. *J. Chem. Phys.* 2016; Vol. 145, DOI: 10.1063/1.4960175.
- (40) Smith, P. E. The alanine dipeptide free energy surface in solution. *J. Chem. Phys.* 1999, 111, 5568–5579.
- (41) Clarke, N. D.; Kissinger, C. R.; Desjarlais, J.; Gilliland, G. L.; Pabo, C. O. Structural studies of the engrailed homeodomain. *Protein Sci.* 1994, 3, 1779–1787.
- (42) Gallagher, T.; Alexander, P.; Bryan, P.; Gilliland, G. L. Two crystal structures of the B1 immunoglobulin-binding domain of streptococcal protein G and comparison with NMR. *Biochemistry* 1994, 33, 4721–4729.
- (43) Vijay-Kumar, S.; Bugg, C. E.; Cook, W. J. Structure of ubiquitin refined at 1.8 Å resolution. *J. Mol. Biol.* 1987, 194, 531–544.
- (44) Huang, Z.; Wu, X.; Luo, R. Isotropic Periodic Sum for Polarizable Gaussian Multipole Model. *J. Chem. Theory Comput.* 2025, 21, 4040–4050.
- (45) University of California, San Francisco, Amber, 2024.
- (46) Hura, G.; Russo, D.; Glaeser, R. M.; Head-Gordon, T.; Krack, M.; Parrinello, M. Water structure as a function of temperature from X-ray scattering experiments and ab initio molecular dynamics. *Phys. Chem. Chem. Phys.* 2003, 5, 1981–1991.
- (47) Kell, G. S. Density, thermal expansivity, and compressibility of liquid water from 0. deg. to 150. deg.. Correlations and tables for atmospheric pressure and saturation reviewed and expressed on 1968 temperature scale. *J. Chem. Eng. Data* 1975, 20, 97–105.
- (48) Malmberg, C.; Maryott, A. Dielectric Constant of Water from 00 to 1000 C. *J. Res. Natl. Bur. Stand.* 1956, 56, 1–8.
- (49) Wagner, W.; Pru, A. The IAPWS formulation 1995 for the thermodynamic properties of ordinary water substance for general and scientific use. *J. Phys. Chem. Ref. Data* 2002, 31, 387–535.
- (50) Archer, D. G.; Carter, R. W. Thermodynamic properties of the NaCl+ H₂O system. 4. Heat capacities of H₂O and NaCl(aq) in cold-stable and supercooled states. *J. Phys. Chem. B* 2000, 104, 8563–8584.