

Isotropic Periodic Sum for Polarizable Gaussian Multipole Model

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Zhen Huang, Xiongwu Wu,* and Ray Luo*



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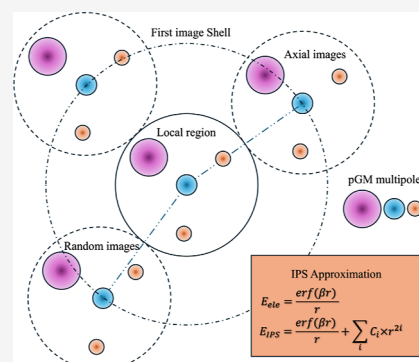


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ABSTRACT: The isotropic periodic sum (IPS) method provides an efficient approach for computing long-range interactions by approximating distant molecular structures through isotropic periodic images of a local region. Here, we present a novel integration of IPS with the polarizable Gaussian multipole (pGM) model, extending its applicability to systems with Gaussian-distributed charges and dipoles. By developing and implementing the IPS multipole tensor theorem within the Gaussian multipole framework, we derive analytical expressions for IPS potentials that efficiently handle both permanent and induced multipole interactions. Our comprehensive validation includes energy conservation tests in the *NVE* ensemble, potential energy distributions in the *NVT* ensemble, structural analysis through radial distribution functions, diffusion coefficients, induced dipole calculations across various molecular systems, and ionic charging free energies. The results demonstrate that the pGM–IPS approach successfully reproduces energetic, structural, and dynamic properties of molecular systems with accuracy comparable to the traditional particle mesh Ewald method. Our work establishes pGM–IPS as a promising method for simulations of polarizable molecular systems, achieving a balance between computational efficiency and accuracy.



INTRODUCTION

Polarizable force fields represent a critical advancement in molecular simulations, offering a more realistic representation of molecular interactions by accounting for the polarization of atoms and molecules in response to their electrostatic environment.^{1–3} Unlike classical force fields, which treat electrostatic interactions as fixed point charges, polarizable force fields enable the modeling of induced dipoles that dynamically adapt to the local environment. This capability is crucial for accurately simulating various chemical and biological processes, particularly those involving strong or fluctuating electric fields, such as ion solvation, protein–ligand binding, and membrane dynamics.

Several approaches have evolved to incorporate polarization into force fields, each striking a different balance between accuracy and computational efficiency. The Drude oscillator model introduces virtual particles representing electron clouds, attached to atomic nuclei by harmonic springs.^{4,5} The fluctuating charge model provides a simpler approach by dynamically adjusting atomic charges based on the local electrostatic environment.⁶ A more sophisticated approach is the induced dipole model, which explicitly calculates induced dipoles at each site through iterative solutions that account for mutual polarization between particles.^{7–11}

The polarizable Gaussian multipole (pGM) model represents an innovative advancement in this field.^{11,12} This model extends the concept of induced dipoles by representing

multipoles as Gaussian distributions rather than point multipoles, which provides a more continuous approximation of electron density compared to delta functions. The Gaussian representation generates a smoother electrostatic potential and can be used to represent the charge penetration effect.¹³ For a detailed pGM formulation, please refer to the Theory Section or our previous paper.¹¹

Recent developments have significantly enhanced the pGM model through improved formulation, optimized algorithms, and efficient MPI parallelization.^{11,14–16} Optimization and validation studies have demonstrated the model's ability to accurately capture polarization effects and its transferability across different molecular environments.^{17–20} The model has been successfully integrated with the restrained electrostatic potential (RESP) fitting for automatic electrostatics fitting and with polarizable continuum model (PCM) calculations to consider solvent effect.^{19,21,22}

To date the pGM model has relied on the particle mesh Ewald (PME) method for calculating long-range electrostatic interactions.^{11,23–26} While PME provides accurate results by

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combining direct space and reciprocal space calculations, it involves significant computational costs, particularly for large systems or high-precision simulations.^{23,25,27} In polarizable models like pGM, these costs are further increased by the iterative self-consistent field approach required to recalculate induced dipoles at each simulation step.

A particular challenge arises in the treatment of induced dipoles within the PME framework. In reciprocal space calculations, the mutual polarization of dipoles necessitates multiple iterations of Fourier transforms to achieve self-consistency, significantly increasing computational overhead. Each iteration requires transforming the electric field between real and reciprocal space, making the process computationally intensive. In contrast, real-space calculations offer a more straightforward approach to handling induced dipoles, as the direct calculation of dipole–dipole interactions can be performed without the need for repeated transformations. This difference in computational efficiency becomes particularly pronounced in large-scale simulations where the cost of multiple Fourier transforms can become a bottleneck.

To address these computational challenges, we have explored the isotropic periodic sum (IPS) method as an alternative approach.^{28–32} The IPS method offers an efficient solution for handling long-range interactions by using isotropic periodic images rather than lattice-based summations. While initially developed for point charge models^{28,32} and later extended to multipole–multipole interactions,³¹ the application of IPS with Gaussian-shaped multipoles remained unexplored until our current work.

In this work, we present the pGM–IPS approach, which extends the IPS method to the polarizable Gaussian multipole model. This novel integration combines the accuracy of Gaussian multipole representation with the computational efficiency of the IPS framework. We validate this approach through rigorous testing, including: energy functional analysis under *NVE* ensemble, energy distribution statistics under *NVT* ensemble, correlation analysis between IPS and PME functionals using identical simulation coordinates, structural properties (such as oxygen–oxygen radial distribution functions in water systems), dynamical properties, induced dipole calculations, and charging free energy calculations. We primarily focus on pure water systems, then gradually extend our analysis to organic solvents and ionic solutions.

METHOD AND ALGORITHM

pGM Formulation. A simple representation of an *n*th order Gaussian multipole with the radius of $1/\beta$ located at $\vec{R}$ is given by

$$\rho^{(n)}(\vec{r}; \vec{R}) = \Theta^{(n)} \cdot \nabla_{\vec{R}}^{(n)} \left(\frac{\beta}{\sqrt{\pi}} \right)^3 \exp(-\beta^2 |\vec{r} - \vec{R}|^2) \quad (1)$$

here the $\Theta^{(n)}$ is the *n*th rank momentum tensor, and $\nabla_{\vec{R}}^{(n)}$ is the *n*th rank gradient operator with respect to position $\vec{R}$. When multipoles are represented as Gaussian distributions, their Coulombic interaction energies, for example, between atom 1 and 2, can be expressed as

$$E^{(n,m)} = (\Theta_1^{(n)} \cdot \nabla_1^{(n)}) (\Theta_2^{(m)} \cdot \nabla_2^{(m)}) \frac{\text{erf}(\beta_{12} R_{12})}{R_{12}} \quad (2)$$

where erf is the error function, and the parameters β_{12} and R_{12} are defined as

$$\beta_{12} = \frac{\beta_1 \beta_2}{\sqrt{\beta_1^2 + \beta_2^2}} \text{ and } R_{12} = |\vec{R}_1 - \vec{R}_2| \quad (3)$$

In the current pGM model, we include both permanent and induced moments up to the dipole order. It should be pointed out that pGM interaction energies depend on the Gaussian radii of both interacting atoms (i.e., atom 1 and 2). For easy integration with existing electrostatics treatments such as PME and IPS, an effective electrostatic potential can be defined at atomic center $\vec{R}_1$ due to permanent multipoles and induced dipoles at atomic center $\vec{R}_2$

$$\phi^{\text{effective}} = (q_2 + \vec{\mu}_2^{\text{perm}} \cdot \nabla_2 + \vec{\mu}_2^{\text{ind}} \cdot \nabla_2) \frac{\text{erf}(\beta_{12} R_{12})}{R_{12}} \quad (4)$$

where β_{12} depends on both atom 1 and 2, q_2 is the permanent charge, $\vec{\mu}_2^{\text{perm}}$ is the permanent dipole, and $\vec{\mu}_2^{\text{ind}}$ is the induced dipole at atomic center $\vec{R}_2$. Such a definition does not change the overall electrostatics energy, but dramatically simplifies the formulation when interfacing with PME as shown in our previous paper.¹¹ For any induced dipole $\vec{\mu}_i^{\text{ind}}$ at atomic center $\vec{R}_i$ is obtained through

$$\vec{\mu}_i^{\text{ind}} = \alpha_i (\vec{E}_i - \sum_{j \neq i}^N \mathbf{T}_{ij} \cdot \vec{\mu}_j^{\text{ind}}) \quad (5)$$

where α_i is the polarizability of atom *i*, and $\vec{E}_i$ is the permanent electric field at atom *i* generated by all other atoms in the system. $\mathbf{T}_{ij}$ is the dipole–dipole interaction tensor, which is defined as

$$\mathbf{T}_{ij} = \partial_i^\alpha \partial_j^\beta \frac{\text{erf}(\beta_{ij} R_{ij})}{R_{ij}} \quad (6)$$

This effective potential formulation eliminates singularities associated with point multipoles and prevents polarization catastrophe by introducing a smooth, finite potential even at short distances.^{33,34}

As shown in the pGM formulation, the charge–charge electrostatic interaction potential can be expressed as

$$e_G(r) = \frac{1}{r} \text{erf}(\beta r) \quad (7)$$

where β is the Gaussian radii, *r* is the pairwise distance. Such interaction potential is the starting point of the derivation of IPS potential.

IPS for Multipolar Systems. In this section, we present the methodology for calculating the electrostatic interaction potential between multipolar systems using the IPS formalism.³¹ In the IPS framework, the total nonbonded potential is expressed as

$$\epsilon_{\text{nonbonded}}^{\text{IPS}}(r, r_c) = \begin{cases} \epsilon_{\text{nonbonded}}(r) + \phi_{\text{nonbonded}}^{\text{IPS}}(r, r_c) & r \leq r_c \\ 0 & r > r_c \end{cases} \quad (8)$$

where r_c represents the cutoff distance. In this formulation, the IPS method approximates the complex nonbonded interaction potential by the original functional within some cutoff distances and corrects that with an IPS potential correction.

It is easy to verify that the m -th order IPS multipole potential, $\varepsilon_{\text{ele}}^{\text{IPSMm}}$, has zero derivatives of up to the $m + 1$ -th order at the boundary

$$\left. \frac{\partial^k}{\partial r^k} (\varepsilon_{\text{ele}}^{\text{IPSMm}}(r, r_c)) \right|_{r=r_c} = 0 \quad (0 < k \leq m + 1) \quad (9)$$

which we call the IPS boundary condition for multipole interactions.

The IPS approach generalizes the interaction between multipoles through the use of a generalized multipole–multipole interaction tensor. The interaction energy is computed as follows

$$E(\mathbf{M}_A^{(i,j,k)}, \mathbf{M}_B^{(t,u,v)}) = (-1)^{i+j+k} \mathbf{M}_A^{(i,j,k)} \cdot \mathbf{T}^{(i+t)(j+u)(k+v)^T} \cdot \mathbf{M}_B^{(t,u,v)} \quad (10)$$

where $\mathbf{M}_A^{(i,j,k)}$ and $\mathbf{M}_B^{(t,u,v)}$ represent the multipole moments for atoms A and B, respectively, and $\mathbf{T}^{(i+t)(j+u)(k+v)^T}$ is the interaction tensor, where the indexes i, j, k, u, v, w represent the order of partial derivatives with respect to the x, y, z directions in Cartesian coordinates. This tensor governs the coupling between these moments and is defined as the derivatives of the base IPS electrostatic potential, $\varepsilon_{\text{ele}}^{\text{IPS}}(r, r_c)$, with respect to Cartesian coordinates. The interaction tensor, T_{tuv} is defined as

$$T_{tuv} = \frac{\partial^t}{\partial x^t} \frac{\partial^u}{\partial y^u} \frac{\partial^v}{\partial z^v} \varepsilon_{\text{ele}}^{\text{IPS}}(r, r_c) \quad (11)$$

This expression calculates the directional dependence of the interaction in three-dimensional space by taking the mixed partial derivatives of the IPS potential with respect to Cartesian coordinates. The interaction tensor T_{tuv} can be factorized into two components: (1) a radial potential vector $\mathbf{S}$ that describes the radial dependence of the interaction, and (2) a directional vector $\mathbf{a}_{tuv}$ that encodes the angular dependence. The factorized form is given by

$$T_{tuv} = \mathbf{a}_{tuv} \cdot \mathbf{S} \quad (12)$$

The factorization allows for efficient computation of the interaction tensor by separating the radial and angular components. The radial potential vector

$$\mathbf{S} = S_0, S_1, S_2, \dots \quad (13)$$

is recursively defined based on the electrostatic potential $\varepsilon_{\text{ele}}(r)$ and its higher-order derivatives. It is computed as follows

$$S_i = \frac{d^{(i)} \varepsilon_{\text{ele}}(r)}{d(r^2/2)^{(i)}} = \begin{cases} \varepsilon_{\text{ele}}(r) & i = 0 \\ \frac{1}{r} \frac{dS_{i-1}}{dr} & i > 0 \end{cases} \quad (14)$$

where $\varepsilon_{\text{ele}}(r)$ is the electrostatic potential function, and higher-order terms S_i are computed by differentiating the preceding terms with respect to r . The recursion provides an efficient means to capture the radial behavior of the interaction. The directional vector

$$\mathbf{a}_{tuv} = (a_0^{(t,u,v)}, a_1^{(t,u,v)}, a_2^{(t,u,v)}, \dots) \quad (15)$$

captures the angular dependence of the interaction and is independent of the radial potential. It can be computed recursively using the following relation

$$a_i^{(t,u,v)} = \sum_{2j \geq t}^i \sum_{2k \geq u}^{i-j} \sum_{2l \geq v}^{i-j-k} c_{2j-t}^{(t)} c_{2k-u}^{(u)} c_{2l-v}^{(v)} x^{2j-t} y^{2k-u} z^{2l-v} \quad (16)$$

$$= \begin{cases} 1 & t + u + v = 0, i = 0 \\ 0 & t + u + v = 0, i > 0 \\ \frac{\partial}{\partial x} a_i^{(t-1,u,v)} + x a_{i-1}^{(t-1,u,v)} & t + u + v > 0, \text{ in } x \\ \frac{\partial}{\partial y} a_i^{(t,u-1,v)} + y a_{i-1}^{(t,u-1,v)} & t + u + v > 0, \text{ in } y \\ \frac{\partial}{\partial z} a_i^{(t,u,v-1)} + z a_{i-1}^{(t,u,v-1)} & t + u + v > 0, \text{ in } z \end{cases} \quad (17)$$

These recursive relations provide a systematic approach for calculating the directional contributions in terms of the Cartesian coordinates. As shown above, the directional contributions $\mathbf{a}_{tuv}$ can be further expanded as polynomials, with the coefficients $c_{2i-n}^{(n)}$ computed using the following relation

$$c_{2i-n}^{(n)} = \begin{cases} \frac{n!}{2^{n-i}(n-i)!(2i-n)!} & 0 \leq 2i-n \leq n \\ 0 & \text{otherwise} \end{cases} \quad (18)$$

The equation defines the constants for the polynomial expansion, enabling the efficient computation of the angular components of the interaction tensor.

Multipole IPS Potential for the pGM Model. The pGM model is designed to account for charge–charge, charge–dipole, and dipole–dipole interactions in molecular systems. To accurately express the total interaction energy, the pGM model requires a second-order IPS multipole potential. This section details the derivation and construction of the multipole potential, along with the recursive methods used to compute higher-order terms.

The total multipole interaction potential can be expressed using a recursive IPS potential formulation. For the m -th order IPS potential, the general form is given by

$$\varepsilon_G^{\text{IPSMm}}(r, r_c) = \begin{cases} \varepsilon_G(r) - S_0(r_c) - \frac{1}{2}(r^2 - r_c^2)S_1(r_c) & m = 0 \\ \varepsilon_G^{\text{IPSM}(m-1)}(r, r_c) - \frac{1}{2^{m+1}(m+1)!}(r^2 - r_c^2)^{m+1} & m > 0 \\ S_{m+1}(r_c) \end{cases} \quad (19)$$

This equation recursively builds the higher-order IPS multipole terms. At each order, the electrostatic potential $\varepsilon_G^{\text{IPS}}$ is corrected by successively adding higher-order derivatives of the potential through the S_i terms, which are functions of the radial coordinate r and the IPS radius r_c .

The pGM model represents that the multipole moments are distributed according to Gaussian functions, which results in the interaction potential being expressed in terms of error functions and their derivatives. This is crucial for describing smooth and long-range interactions in molecular systems.

The radial potential vector, $\mathbf{S}$, for the pGM model is computed through a recursive differentiation process, starting from the zeroth-order term S_0 . The expressions for the first few terms of the radial potential vector are provided below

$$S_0 = \varepsilon_G(r) = \frac{1}{r} \text{erf}(\beta r) \quad (20)$$

$$S_1 = \frac{1}{r} \frac{d}{dr} S_0 = -\frac{1}{r^3} \left(\text{erf}(\beta r) - \frac{2\beta r}{\sqrt{\pi}} e^{-\beta^2 r^2} \right) \quad (21)$$

$$S_2 = \frac{1}{r} \frac{d}{dr} S_1 = \frac{1}{r^5} \left(3\text{erf}(\beta r) - \frac{6\beta r + 4\beta^3 r^3}{\sqrt{\pi}} e^{-\beta^2 r^2} \right) \quad (22)$$

$$S_3 = \frac{1}{r} \frac{d}{dr} S_2 = -\frac{1}{r^7} \left(15\text{erf}(\beta r) - \frac{30\beta r + 20\beta^3 r^3 + 8\beta^5 r^5}{\sqrt{\pi}} e^{-\beta^2 r^2} \right) \quad (23)$$

$$S_4 = \frac{1}{r} \frac{d}{dr} S_3 = \frac{1}{r^9} \left(105\text{erf}(\beta r) - \frac{210\beta r + 140\beta^3 r^3 + 56\beta^5 r^5 + 16\beta^7 r^7}{\sqrt{\pi}} e^{-\beta^2 r^2} \right) \quad (24)$$

These expressions define the first few terms in the series expansion of the radial potential vector. Each S_i term introduces higher-order corrections to the potential, and these corrections are essential for capturing the interactions between higher-order multipoles in the pGM model. The second order IPS multipole interactions for pGM needs only S_0 , S_1 , S_2 , and S_3 , because all direction vectors have zero components for elements $i = 4$ and higher, as shown in Table 1.

Table 1

$a_{(0,0,0)} = (1, 0, 0, 0, 0, \dots)$	$a_{(0,1,0)} = (0, x, 0, 0, 0, \dots)$	$a_{(0,0,1)} = (0, z, 0, 0, 0, \dots)$
$a_{(2,0,0)} = (0, 1, x^2, 0, 0, \dots)$	$a_{(0,2,0)} = (0, 1, y^2, 0, 0, \dots)$	$a_{(0,0,2)} = (0, 1, z^2, 0, 0, \dots)$
$a_{(1,1,0)} = (0, 0, xy, 0, 0, \dots)$	$a_{(1,0,1)} = (0, 0, xz, 0, 0, \dots)$	$a_{(0,1,1)} = (0, 0, yz, 0, 0, \dots)$
$a_{(3,0,0)} = (0, 0, 3x, x^3, 0, \dots)$	$a_{(0,3,0)} = (0, 0, 3y, y^3, 0, \dots)$	$a_{(0,0,3)} = (0, 0, 3z, z^3, 0, \dots)$
$a_{(2,1,0)} = (0, 0, y, x^2y, 0, \dots)$	$a_{(2,0,1)} = (0, 0, z, x^2z, 0, \dots)$	$a_{(1,2,0)} = (0, 0, x, y^2x, 0, \dots)$
$a_{(0,2,1)} = (0, 0, z, y^2z, 0, \dots)$	$a_{(1,0,2)} = (0, 0, x, z^2x, 0, \dots)$	$a_{(0,1,2)} = (0, 0, y, z^2y, 0, \dots)$
$a_{(1,1,1)} = (0, 0, 0, xyz, 0, \dots)$		

The second-order IPS potential, which incorporates dipole–dipole interactions via its second derivative, is expressed as

$$\varepsilon_G^{\text{IPS2}}(r, r_c) = \frac{1}{r} \text{erf}(\beta r) + A_2 + B_2 r^2 + C_2 r^4 + D_2 r^6 \quad (25)$$

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

$$A_2 = -\frac{1}{48r_c} \left(105\text{erf}(\beta r_c) - \frac{114\beta r_c + 44\beta^3 r_c^3 + 8\beta^5 r_c^5}{\sqrt{\pi}} e^{-\beta^2 r_c^2} \right) \quad (26)$$

$$B_2 = \frac{1}{48r_c^3} \left(105\text{erf}(\beta r_c) - \frac{210\beta r_c + 108\beta^3 r_c^3 + 24\beta^5 r_c^5}{\sqrt{\pi}} e^{-\beta^2 r_c^2} \right) \quad (27)$$

$$C_2 = -\frac{1}{48r_c^5} \left(63\text{erf}(\beta r_c) - \frac{126\beta r_c + 84\beta^3 r_c^3 + 24\beta^5 r_c^5}{\sqrt{\pi}} e^{-\beta^2 r_c^2} \right) \quad (28)$$

$$D_2 = \frac{1}{48r_c^7} \left(15\text{erf}(\beta r_c) - \frac{30\beta r_c + 20\beta^3 r_c^3 + 8\beta^5 r_c^5}{\sqrt{\pi}} e^{-\beta^2 r_c^2} \right) \quad (29)$$

The second-order IPS potential offers a robust representation of the pGM potential, capturing both short- and long-range interactions with higher accuracy. The recursive nature of the potential calculation allows for easy extension to higher-order multipoles.

To visualize the potentials, the behavior of the Gaussian electrostatic potential and IPS2 potential are shown in the figure below (Figure 1).

Simulation Details and Code Availability. All simulations were performed using the sander³⁵ MD engine in AMBER 24,³⁶ with the implementation scheduled for release in AMBER 25. Our validation of the pGM–IPS method encompassed several molecular systems. The benchmark system consisted of 512 water molecules in a truncated-octahedral box with a side length of 27 Å. To evaluate the method's performance with induced dipoles, we extended our analysis on four organic solvents: methyl isocyanate, methyl nitrite, ethanol, and propanol. We further examined NaCl ionic systems in aqueous solution. The electrostatic-related parameters are parametrized using PyRESP,²² while all van der Waals parameters are retained from the existing model without modification. All initial configurations were generated using tLEaP from the AMBER 24 package.³⁶ All simulation parameters and input files are available at <https://github.com/larryhuang98/pgm-ips.git>, with detailed simulation and analysis information provided in Section S2.

Trajectory analysis was conducted using CPPTRAJ from AMBER, complemented by custom Python scripts developed with NumPy and SciPy packages.^{37,38}

RESULTS AND DISCUSSION

Energy Conservation in NVE Simulation. A correct implementation for any potential function in molecular dynamics is its ability to conserve energy in an NVE simulation. This criterion is particularly crucial for polarizable force fields, as they aim to provide a more accurate and dynamic representation of molecular interactions by allowing polarization effects to vary with the molecular environment.

In polarizable force fields, such as those using induced dipoles, inaccuracies in calculating these dipoles during multipole–multipole interactions can easily lead to energy drift, often resulting in a progressively decreasing total energy.³⁹ Such drift is problematic, as it may mask or distort the actual physical behavior of the simulated system, leading to unreliable conclusions. Figure 2 shows the total energy profiles and corresponding energy drift for both the IPS and PME methods, applying the same convergence tolerance for mutual dipole iterations. It is crucial to highlight that the energy drifts reported here are raw outputs from AMBER without any corrections using a shadow Hamiltonian, providing an unaltered view of the methods' performance.

For the PME method, we employed a high-precision setup, including an eighth-order B-spline interpolation to accurately represent the reciprocal mesh charges and dipoles. This setup is designed to maximize the accuracy of the electrostatic interactions, ensuring minimal numerical error. To effectively

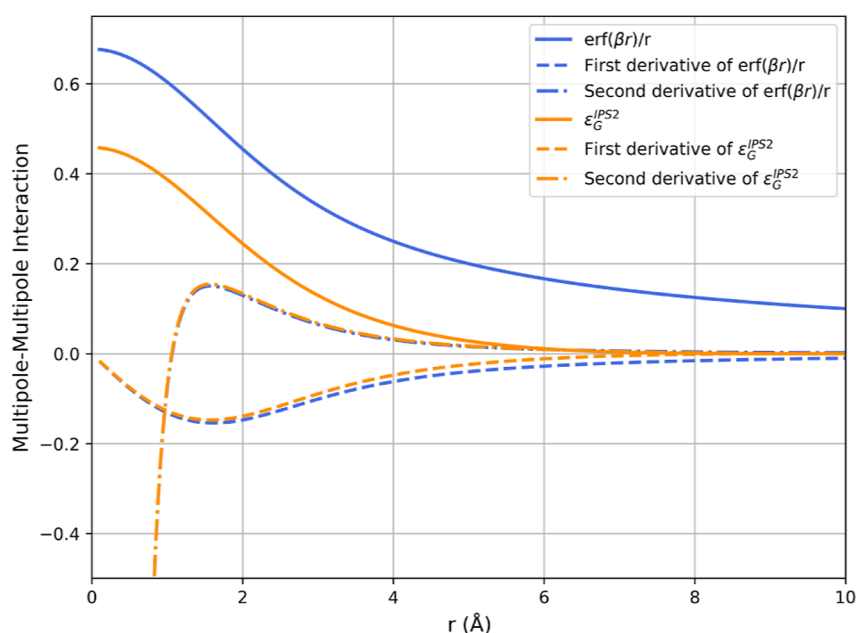


Figure 1. Comparison of the Gaussian electrostatic potential and IPS multipole potential with a cutoff distance $r_c = 10$ Å.

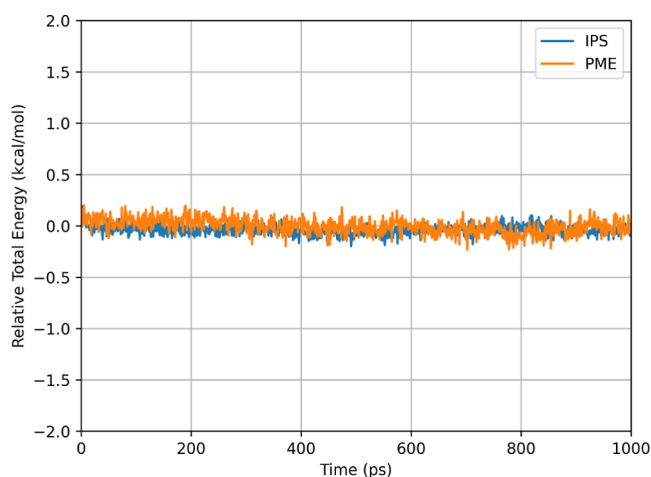


Figure 2. Comparison of energy drift between IPS and PME methods over a 1 ns NVE simulation. The IPS method exhibits an energy drift of 2.03×10^{-4} kcal/mol, while the PME method shows a drift of 1.67×10^{-4} kcal/mol. Both methods demonstrate comparable energy conservation, indicating that IPS is a viable alternative to PME for polarizable simulations.

capture polarization effects in the IPS method, we utilized a multipole potential with a second-order expansion, aiming to

strike a balance between computational efficiency and accuracy.

Despite these stringent settings, our simulations revealed that minor energy drifts still occur in the PME method. Specifically, the energy drift for PME over a 1 ns simulation period was recorded at 1.67×10^{-4} kcal/mol. The time step is 1 fs. This small drift is consistent with minor numerical inaccuracies that are inherent in the PME method, yet generally acceptable for maintaining energy conservation in practice.

In comparison, the IPS method, as shown in Figure 2, demonstrates a comparable energy conservation performance, with an energy drift of 2.03×10^{-4} kcal/mol over the same simulation duration. Although this represents a slightly higher drift (0.36×10^{-4} kcal/mol more than PME), the small deviation is within acceptable limits for high-resolution molecular dynamics simulations. This finding highlights that the IPS method can achieve a similar level of energy conservation as PME, making it a robust alternative, particularly for simulations that require a balance between accuracy and computational efficiency.

Potential Energy Distribution in NVT Simulation.

Beyond NVE simulations, validating the potential energy distribution in the NVT ensemble is essential for ensuring the practical applicability of the IPS method. The NVT ensemble, where temperature and volume are held constant, is a common

Table 2. Comparison of IPS and PME Potential Energies at Different Cutoff Values, Highlighting the Differences and Percentage Deviations Relative to PME^a

cutoff (Å)	6	7	8	9	10
IPS (kcal/mol)	−504891.25	−504824.19	−504837.81	−504833.86	−504799.10
PME (kcal/mol)	−504602.56	−504673.45	−504670.26	−504671.93	−504679.38
difference (kcal/mol)	−288.69	−150.73	−167.56	−161.93	−119.72
percentage difference	−0.0572%	−0.0299%	−0.0331%	−0.0321%	−0.0237%
difference per atom	−0.1878	−0.0981	−0.1090	−0.1054	−0.0779

^aThese results indicate that the IPS method produces comparable energy values across different cutoffs, demonstrating its effectiveness and accuracy in NVT simulations.

setup for simulating molecular systems as it allows for the assessment of thermal equilibrium and stability over time. To this end, we compare the potential energy averages and fluctuations of the IPS and PME methods for a water system simulated under *NVT* conditions, as shown in Tables 2 and 3.

Table 3. Comparison of IPS and PME Energy Fluctuations at Different Cutoff Values under the Berendsen Thermostat^a

cutoff (Å)	6	7	8	9	10
IPS fluctuation (kcal/mol)	27.30	27.20	28.52	27.30	28.23
PME fluctuation (kcal/mol)	30.87	28.46	27.36	27.47	27.31

^aThe comparable fluctuations indicate that the IPS method achieves similar energy stability to PME, supporting its use in *NVT* simulations.

Table 2 provides the potential energy values obtained for the IPS and PME methods across different cutoff distances, ranging from 6 to 10 Å. At a cutoff of 6 Å, the potential energy for IPS is −504891.25 kcal/mol, while PME records a value of −504602.56 kcal/mol, resulting in a difference of −288.69 kcal/mol. This difference corresponds to a percentage deviation of −0.0572%. As the cutoff distance increases, the deviations become progressively smaller, demonstrating that the IPS method's potential energies converge toward those of PME. For example, at a cutoff of 10 Å, the potential energy difference between IPS and PME is reduced to −119.72 kcal/mol, with a percentage deviation of −0.0237%. These results indicate that the IPS method achieves a level of convergence similar to PME, underscoring its accuracy and reliability across varying cutoff distances.

Additionally, we evaluated the potential energy fluctuations for IPS and PME under the *NVT* ensemble using the Berendsen thermostat,⁴⁰ as shown in Table 3. At a cutoff of 6 Å, the energy fluctuation for IPS is 27.30 kcal/mol, while for PME, it is 30.87 kcal/mol. This indicates a deviation of 3.57

kcal/mol between the two methods. However, as the cutoff is increased to 10 Å, the energy fluctuations for IPS (28.23 kcal/mol) and PME (27.31 kcal/mol) become almost identical, with a deviation of less than 1 kcal/mol. This convergence across cutoffs confirms that the IPS method is capable of maintaining thermal equilibrium in a manner consistent with PME, even under varying cutoff distances.

The consistent reduction in differences between IPS and PME values as the cutoff distance increases highlights the robustness of the IPS method. By achieving comparable potential energy values and fluctuations to PME, the IPS method demonstrates its viability as a reliable alternative for conducting detailed molecular dynamics simulations, especially when computational efficiency and scalability are essential.

To further substantiate the consistency between IPS and PME, we conducted a frame-by-frame comparison of potential energies obtained from PME simulations, evaluated with the IPS method. The results, shown in Figure 3, indicate a near-perfect correlation of 0.9997. This high level of agreement suggests that the IPS method can accurately reproduce the energy values obtained from PME simulations. The small differences in energy values between the two methods are due to certain constant terms not fully considered by the current PME implementation, particularly the Gaussian–Gaussian self-energy terms. Despite these minor discrepancies, the strong correlation curve underscores the robustness of the IPS method as a practical and scalable alternative for molecular dynamics simulations.

Radial Distribution Functions. Radial distribution functions (RDFs) are critical tools for evaluating the structure and spatial arrangement of particles in molecular dynamics simulations. They are highly sensitive to the underlying potential functions, making them a reliable metric for assessing the accuracy of different simulation methods. In cutoff-based methods, such as the IPS approach, abnormal deviations can often occur around the cutoff boundary, leading to discrepancies when compared to full-range methods like particle mesh Ewald.

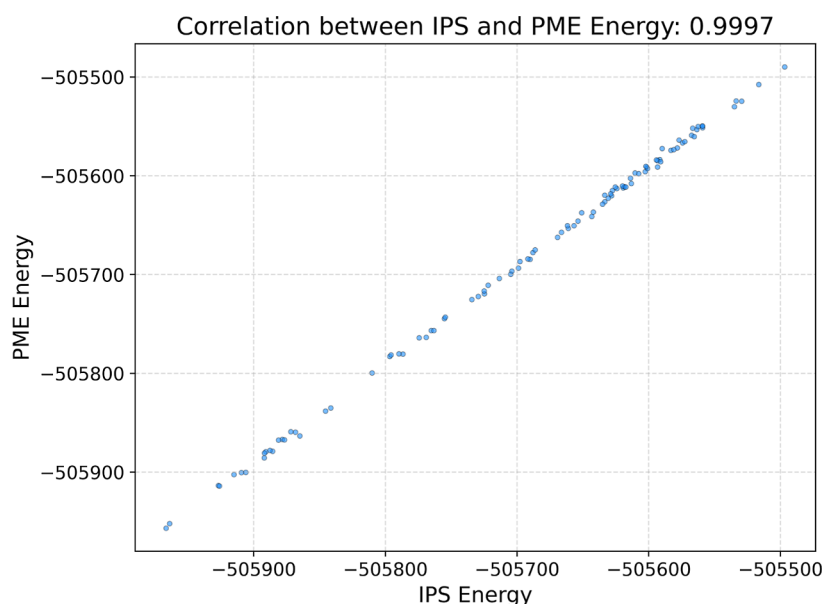


Figure 3. Correlation between potential energies obtained using the IPS and PME methods under *NVT* conditions. The high correlation value (0.9997) indicates that IPS can accurately reproduce the energy properties of PME, confirming its reliability across varying configurations.

To quantify the accuracy of the IPS method in reproducing the PME RDFs, we calculate the root-mean-square deviations (RMSDs) of the RDFs obtained using the IPS method relative to those generated by high standard PME method. The RMSD values defined below provide a direct measure of how closely the IPS method matches the structural information captured by PME, highlighting its effectiveness or limitations at different cutoff distances.

$$\text{RMSD} = \sqrt{\frac{1}{N_g} \sum_i (g(r_i) - g_{\text{PME}}(r_i))^2} \quad (30)$$

where N_g is the number of data points in the calculated RDF, with a cutoff of 10 Å and an interval of 0.001 Å.

Table 4 shows the RMSDs for the RDFs across various cutoff distances, comparing the performance of the IPS

Table 4. Root-Mean-Square Deviations (RMSDs) of RDFs for the IPS Method Relative to PME at Various Cutoff Distances^a

cutoff (Å)	6	7	8	9	10
IPS RMSD	0.041778	0.019717	0.011396	0.009312	0.008491
PME RMSD	0.022030	0.008328	0.008260	0.008231	0.000000

^aLower RMSD values indicate better agreement with PME RDFs, demonstrating improved structural accuracy as the cutoff increases.

method with PME. Here, we set the PME method with 10 Å as a benchmark. At a cutoff of 6 Å, the RMSD for the IPS method is 0.0418, which, while larger than PME's 0.0220, is still within an acceptable range, demonstrating that IPS performs reasonably well even at shorter cutoffs. As the cutoff distance increases, the RMSD for IPS decreases significantly, reaching 0.0085 at a cutoff of 10 Å, where it closely approximates the PME result. The complete RDF plots comparing IPS and PME methods for water systems are provided in Supporting Information (Figures S1–S5), offering visual confirmation of these numerical comparisons.

These results indicate that the IPS method is highly effective in reproducing RDFs, particularly at larger cutoffs. Even at smaller cutoffs, where deviations are slightly higher, the accuracy remains acceptable for practical simulations. The close agreement between IPS and PME at higher cutoffs, especially at 10 Å, confirms that IPS can provide a reliable and computationally efficient alternative to PME for molecular dynamics simulations.

Diffusion Coefficients. The diffusion coefficient is a key parameter for characterizing the dynamical behavior of a

molecular system, providing insights into how molecules move and interact over time. In this study, we compute the diffusion coefficients using the velocity autocorrelation function (VACF), which captures the time-dependent nature of particle velocities and their correlations.

The VACF describes how the velocity of a particle at a given time is related to its velocity at a later time, offering insights into the particle's motion and the system's overall dynamical properties. By integrating the VACF over time, we can directly compute the diffusion coefficient, D , using the Green–Kubo relation⁴¹

$$D = \frac{1}{3} \int_0^\infty \langle \vec{v}(t) \cdot \vec{v}(0) \rangle dt \quad (31)$$

where $\vec{v}(t)$ is the velocity of a particle at time t , and $\langle \vec{v}(t) \cdot \vec{v}(0) \rangle$ represents the autocorrelation of the velocity. This approach provides a reliable estimate of the diffusion coefficient, reflecting the true dynamical behavior of the system.

Table 5 presents the average diffusion coefficients obtained using both IPS and PME methods, along with their fluctuations across 10 runs for different cutoff values. For cutoff distances of 6–10 Å, the IPS average diffusion coefficients range from 0.212 to 0.303 Å²/ps, with corresponding fluctuations between 0.034 and 0.051 Å²/ps. The PME method shows slightly higher values, ranging from 0.273 to 0.337 Å²/ps, with fluctuations between 0.038 and 0.056 Å²/ps.

The diffusion coefficient for water at room temperature from experimental measurements is approximately 0.23 Å²/ps.⁴² The IPS diffusion coefficients show particularly good agreement with this experimental value at cutoffs of 6 and 10 Å, where the average diffusion constants are 0.212 and 0.246 Å²/ps, respectively. In comparison, the PME method tends to slightly overestimate the diffusion coefficient, with values ranging from 0.273 to 0.337 Å²/ps across different cutoffs.

The fluctuations in the diffusion coefficient, represented by the standard deviation values in Table 5, indicate the variability across the 10 runs. For the IPS method, the lowest fluctuation occurs at a cutoff of 6 Å (0.034 Å²/ps), while the highest fluctuation is observed at a cutoff of 10 Å (0.051 Å²/ps). The PME method shows similar variability, with fluctuations ranging from 0.038 to 0.056 Å²/ps. The larger fluctuations at higher cutoffs may be related to the increased computational complexity and interactions that come into play with larger cutoff distances.

Overall, while both methods provide reasonable estimates of water diffusion coefficients, the IPS method demonstrates particularly good agreement with experimental data, especially at certain cutoff distances. This makes IPS a suitable alternative to PME for dynamic simulations of water systems, where diffusion properties are important.

Table 5. Comparison of Diffusion Constants between IPS (with Different Cut-Off Distance Values) and PME Methods Relative to the Experimental Value of 0.23 Å²/ps^{42a}

cutoff distance (Å)	6	7	8	9	10
IPS average (Å ² /ps)	0.212379	0.286751	0.303162	0.265326	0.246475
IPS error (%)	−7.7	24.7	31.8	15.4	7.2
IPS fluctuation (Å ² /ps)	0.034814	0.040985	0.050444	0.045423	0.051793
PME average (Å ² /ps)	0.337058	0.303020	0.275595	0.279372	0.273281
PME error (%)	46.5	31.7	19.8	21.5	18.8
PME fluctuation (Å ² /ps)	0.055862	0.045307	0.045989	0.038446	0.048359

^aError is calculated as (method − experimental)/experimental × 100%.

Induced Dipole Calculation. The pGM model inherently relies on induced dipoles to represent polarization effects. Therefore, one important way to validate the accuracy of this method is by computing the induced dipoles for selected systems. In this section, we compute the induced dipoles for a pure water model and investigate four organic solvent systems: methyl isocyanate (CH_3NCO), methyl nitrite (CH_3ONO), ethanol ($\text{CH}_3\text{CH}_2\text{OH}$), and propanol ($\text{CH}_3\text{CH}_2\text{CH}_2\text{OH}$). Each organic solvent is studied as a bulk liquid system to evaluate how well the pGM model captures the local polarization effects in different molecular environments.

We begin by examining the induced dipoles in a pure water system, comparing results between the IPS and PME methods. Table 6 presents both the component-wise (x, y, z) and scalar

Table 6. Comparison of Induced Dipoles between IPS and PME Methods for the Water System^a

quantity	IPS (eÅ)	PME (eÅ)	difference (eÅ)
average induced dipole	0.435612	0.436352	-7.40×10^{-4}
overall STD	0.038412	0.039318	-9.06×10^{-4}
X-component average	-0.038042	-0.037969	-7.3×10^{-5}
X-component STD	0.232646	0.233030	-3.85×10^{-4}
Y-component average	-0.006741	-0.006743	2.0×10^{-6}
Y-component STD	0.266659	0.267281	-6.21×10^{-4}
Z-component average	-0.022625	-0.022610	-1.5×10^{-5}
Z-component STD	0.252978	0.253394	-4.16×10^{-4}
average scalar difference		5.82×10^{-3}	

^aThe table presents average induced dipole moments and their standard deviations (STD) in eÅ, organized by overall magnitude and directional components.

differences in the induced dipoles between the two methods. This comparison establishes a baseline for validating the consistency of induced dipole calculations using the IPS approach. For this calculation, we use the molecular dipole moment averaged across all water molecules in the first simulation frame.

The results demonstrate that the induced dipole values calculated using the IPS method are in close agreement with those from the PME method for the water system. The average induced dipole for the IPS method is 0.4356 eÅ, compared to 0.4364 eÅ for PME. The differences in the x , y , and z components of the induced dipole are minimal, with an average scalar difference of 0.0058 eÅ, indicating a high level of consistency between the two methods.

For the organic solvent systems, we compare the molecular induced dipole moments calculated using both PME and IPS methods. The induced dipole results are molecular induced dipoles averaged across all organic molecules in the system. The results are presented in Table 7.

The comparison across these organic solvent systems enables a thorough evaluation of the pGM-IPS method's performance in different chemical environments. The analysis spans molecules with varying functional groups, including isocyanate, nitrite, and hydroxyl groups, as well as different carbon chain lengths. This diverse set of molecular environments provides a comprehensive test of the method's ability to accurately capture polarization effects in bulk organic liquids. The results demonstrate the robustness of the pGM-IPS approach in handling various chemical environments while maintaining computational efficiency.

Table 7. Comparison of Molecular Dipoles between IPS and PME Methods for Organic Solvent Systems^a

molecule & quantity	IPS (eÅ)	PME (eÅ)	difference (eÅ)
methyl isocyanate average	0.193997	0.193843	1.54×10^{-4}
methyl isocyanate STD	0.031983	0.034464	-2.48×10^{-3}
methyl nitrite average	0.190174	0.190760	-5.86×10^{-4}
methyl nitrite STD	0.031000	0.032688	-1.69×10^{-3}
ethanol average	0.216243	0.217683	-1.44×10^{-3}
ethanol STD	0.048880	0.049767	-8.87×10^{-4}
propanol average	0.228608	0.229965	-1.36×10^{-3}
propanol STD	0.046808	0.048289	-1.48×10^{-3}

^aThe table presents average molecular dipole moments and their standard deviations (STD) in eÅ for different molecules.

One other interesting system is the ionic in the water systems. Here we present results with our Na–Cl ions in water. The difficulty of such systems lies in the fact that ions can introduce strong local electric fields and significant polarization effects, presenting a more stringent test for electrostatic methods. Specifically, we set up our system with 4 pairs of Na–Cl ions inside a $26.291 \times 26.194 \times 25.698$ Å rectangular box containing 612 water molecules. The resulting ion concentration is approximately 0.36 M, representing a moderately concentrated electrolyte solution. The induced dipoles presented here represent the specific values at each ionic atom in the first simulation frame, not averaged across multiple atoms.

The induced dipoles for both Na^+ and Cl^- ions show excellent agreement between the PME and IPS methods, as shown in Table 8. Several interesting features emerge from this

Table 8. Comparison of Induced Dipoles between PME and IPS Methods for Na^+ and Cl^- Ions in Water

ion	PME (eÅ)	IPS (eÅ)	difference (eÅ)
Na_1^+	0.00477	0.00469	8.0×10^{-5}
Na_2^+	0.00322	0.00295	2.7×10^{-4}
Na_3^+	0.00277	0.00274	3.0×10^{-5}
Na_4^+	0.00110	0.00112	-2.0×10^{-5}
Cl_1^-	0.0773	0.0739	3.4×10^{-3}
Cl_2^-	0.2030	0.2037	-7.0×10^{-4}
Cl_3^-	0.2421	0.2402	1.9×10^{-3}
Cl_4^-	0.2916	0.2804	1.1×10^{-2}

data: First, the Cl^- ions exhibit significantly larger induced dipoles (0.074–0.292 eÅ) compared to Na^+ ions (0.001–0.005 eÅ), which is expected due to the larger polarizability of chloride ions. Second, there is notable variation in the induced dipoles among different ions of the same species, reflecting their distinct local environments in the solution. The differences between PME and IPS methods remain small throughout, with the largest deviation being 0.0112 eÅ for one of the Cl^- ions, demonstrating that IPS can accurately capture the polarization effects even in these challenging ionic systems.

Decharging Solvation Free Energy. Free energy calculations represent one of the most stringent tests for force field accuracy, particularly for evaluating electrostatic interactions in ionic systems. The ability to accurately reproduce solvation free energies is crucial for modeling various biological and chemical processes, from ion transport to protein–ligand binding.^{43–47} We therefore conducted

Table 9. Window-by-Window Comparison of De-Charging Free Energies (kcal/mol) between PME and IPS Methods

λ window	PME ΔG	IPS ΔG	difference	% difference
1.0 $\rightarrow$ 0.9	37.950 $\pm$ 0.006	37.022 $\pm$ 0.008	0.928	2.44
0.9 $\rightarrow$ 0.8	34.025 $\pm$ 0.007	33.846 $\pm$ 0.006	0.179	0.53
0.8 $\rightarrow$ 0.7	29.782 $\pm$ 0.010	30.125 $\pm$ 0.009	−0.343	−1.15
0.7 $\rightarrow$ 0.6	24.980 $\pm$ 0.009	25.232 $\pm$ 0.009	−0.252	−1.01
0.6 $\rightarrow$ 0.5	20.782 $\pm$ 0.008	20.754 $\pm$ 0.008	0.028	0.13
0.5 $\rightarrow$ 0.4	15.739 $\pm$ 0.011	15.892 $\pm$ 0.010	−0.153	−0.97
0.4 $\rightarrow$ 0.3	11.503 $\pm$ 0.009	11.283 $\pm$ 0.008	0.220	1.91
0.3 $\rightarrow$ 0.2	8.000 $\pm$ 0.009	7.761 $\pm$ 0.007	0.239	2.99
0.2 $\rightarrow$ 0.1	4.494 $\pm$ 0.008	4.530 $\pm$ 0.006	−0.036	−0.80
0.1 $\rightarrow$ 0.0	1.335 $\pm$ 0.008	1.332 $\pm$ 0.006	0.003	0.22
total	188.589 $\pm$ 0.027	187.776 $\pm$ 0.024	0.813	0.43

decharging free energy calculations to further validate the IPS method against PME results.⁴⁸

The decharging free energy is one component of the alchemical free energy calculation pathway, specifically focusing on gradually eliminating the electrostatic interactions. While a complete alchemical process typically involves both decharging and the removal of van der Waals interactions using softcore potentials, we focused solely on the electrostatic component since our goal was to validate the IPS method's electrostatic treatment in comparison with PME. The decharging free energy calculation was designed using a process parameter λ to screen the charge and polarizability of ions, implementing 11 windows from $\lambda = 1.0$ to $\lambda = 0.0$ with intervals of 0.1. Starting from $\lambda = 1.0$, which represents the original parameters of the NaCl in water, we ran 2 ns for each window, with 1 ns as the equilibration phase and the final 1 ns as the production phase. Each subsequent window restarted from the restart file of the previous window.

After the simulations, we evaluated the energy of each configuration using both its own and the neighboring windows' topological parameters. The collected data were combined, and the Bennett acceptance ratio (BAR)⁴⁹ method was used to calculate the free energy differences between neighboring windows, as shown in Table 9. The window-by-window comparison reveals that the largest deviation occurs at the fully charged state ($\lambda = 1.0 \rightarrow 0.9$) with a difference of 0.928 kcal/mol (2.44%). The differences become notably smaller in the intermediate windows, and excellent agreement is achieved in the final stages of decharging. The total decharging free energy calculated using PME was 188.589 $\pm$ 0.027 kcal/mol, while IPS yielded 187.776 $\pm$ 0.024 kcal/mol. The overall difference of 0.813 kcal/mol (0.43%) between the two methods demonstrates excellent agreement, indicating that IPS accurately reproduces the electrostatic behavior of the PME method in free energy calculations.

CONCLUSION

In this study, we have evaluated the IPS method applied to the pGM model in molecular dynamics simulations. Through a series of comprehensive tests, the IPS method was shown to be a robust alternative to the widely used PME approach for handling long-range electrostatic interactions in polarizable systems.

One of the most critical tests in our evaluation was the examination of energy conservation in the NVE ensemble. The IPS method demonstrated its ability to conserve energy effectively, with an energy drift that closely mirrors that observed in PME simulations. This suggests that IPS is capable

of providing stable integration over long simulation times, a key requirement for accurate molecular dynamics simulations. In the NVT ensemble, IPS also performed consistently, with potential energy distributions that were highly comparable to PME, validating its reliability in sampling canonical ensembles.

From a structural perspective, the RDFs calculated using IPS showed excellent agreement with those derived from PME. This result confirms the capability of the IPS method to accurately capture the spatial arrangement of molecules, including the detailed structure of solvation shells. The ability to reproduce such fine structural details highlights the accuracy of IPS in resolving intermolecular interactions, which is crucial for understanding system behavior at the atomic level.

The analysis of diffusion coefficients further demonstrated that IPS can accurately capture the dynamic properties of the system. The water diffusion coefficients calculated with IPS were consistent with those obtained from PME, indicating that IPS can reliably model molecular mobility and dynamic behavior. This consistency across both structural and dynamic properties underlines the versatility of the IPS method in a range of simulation conditions.

The accuracy of the induced dipole moments calculated with the pGM model was another important aspect of this work. The induced dipoles, computed with IPS, closely matched those obtained using PME, as well as theoretical and experimental reference values. This is particularly significant given the sensitivity of polarizable models to the treatment of long-range interactions, and it reinforces the conclusion that IPS is a reliable method for such systems.

The decharging free energy calculations provided perhaps the most stringent test of the method's accuracy. The excellent agreement between IPS and PME in these calculations, with only 0.43% difference in total free energy, demonstrates that IPS can accurately capture the thermodynamic properties of complex systems. This agreement extends across the entire charging/decharging pathway, with particularly good consistency in the intermediate charging states.

Overall, the IPS method, combined with the pGM model, has proven to be a competitive alternative to PME, offering accurate and reliable simulations of molecular systems with polarizable force fields. While IPS matches PME in terms of energy conservation, structural accuracy, and dynamic properties, it holds potential for further optimization in computational efficiency, particularly in large-scale and high-performance computing environments. In the current stage of development, we aim to validate that the IPS method has solid theoretical background and produces similar results as the PME method. We provide a timing test in Supporting

Information Table S1, where we run 1000 steps for a 4096 water box. The test show that even if the code has not been optimized, it outperforms the PME method in a 4-core parallel run by 12% while using 8 cores, it outperforms 16% and for 16 cores, it is faster by 40%. As more cores are used, the PME runs are not that well parallelized while IPS maintains its parallelization efficiency. Future work will focus on enhancing the scalability of IPS and expanding its application to more diverse and complex molecular systems, with the goal of maintaining its high accuracy while reducing computational costs.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.jctc.5c00123>.

Scaling timing test between IPS and PME method (Table S1), along with RDF plots (Figures S1–S5). Section S1 shows the simulation details for each parts of simulation (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Xiongwu Wu – Laboratory of Computational Biology, NHLBI, NIH, Bethesda, Maryland 20892, United States; Email: wuxw@nhlbi.nih.gov

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

Author

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

Complete contact information is available at:

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Notes

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