

*Overview of a new **Image-Charge Solvation Model (ICSM)** for Electrostatic Interactions*

Donald Jacobs

UNC Charlotte, Department of Physics and Optical Science

People involved in developing ICSM --- A group project

Professors

Postdocs

Students

²Wei Cai

¹Yuchun Lin

²Peihua Qin

¹Wei Song

²Shaozhong Deng

²Zhenli Xu

²Ming Xiang

¹Shira Stav

¹Andrij Baumketner

¹Boris Ni

²Kathy Baker

¹Department of Physics and Optical Science

²Department of Mathematics and Statistics

Funding

NIH NIGMS R01GM083600

OUTLINE

INTRODUCTION

- **Motivation: Need for a explicit/implicit hybrid model**
- **Reaction field from solvent using multiple image charges**
- **Simulation setup for all-atom molecular dynamics**

RESULTS

- **Properties of bulk water (0 ionic strength)**
- **Ion solvation (Na^+ , $\text{Na}^+\text{-Cl}^-$, $\text{Na}^+\text{-Na}^+$, $\text{Cl}^-\text{-Cl}^-$)**
- **Improved image charge formulas**

CONCLUSIONS

- **Software implementation for TINKER**

Introduction

- **Electrostatic interactions play an essential role in the stability and function of biopolymers such as **proteins**.**
- **Different computational methods offer different types of accuracy versus efficiency tradeoffs.**

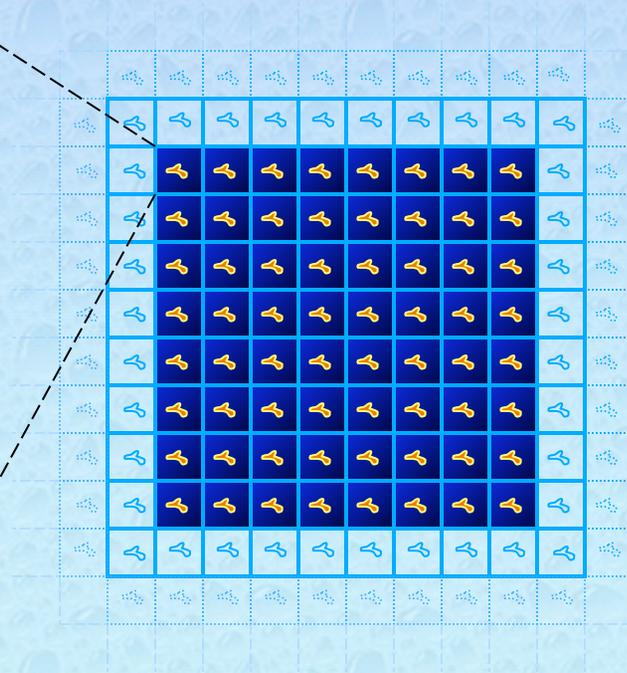
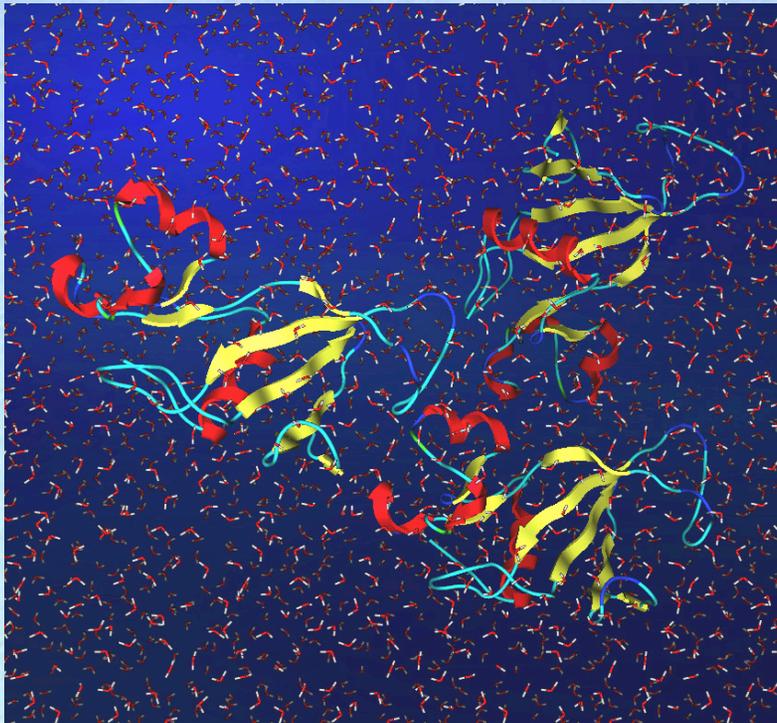
Two commonly employed types of methods:

- **(explicit)** All-atom model using periodic boundary conditions.
- **(implicit)** Continuum solvent model that treats solvent as a dielectric medium.

Explicit Solvent Models

In all-atom simulations, the solvent is treated as a collection of molecules/atoms.

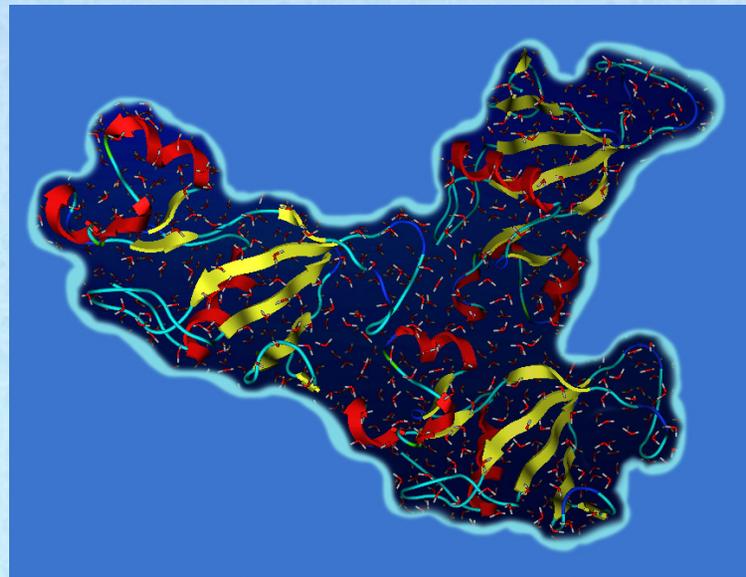
- **Strengths:** High accuracy when using PBC.
- **Weaknesses:** Need large unit cells that are computationally intensive for biologically relevant timescales.



Implicit Solvent Models

The solvent is represented as a dielectric continuum and the biopolymer is placed in a low dielectric medium.

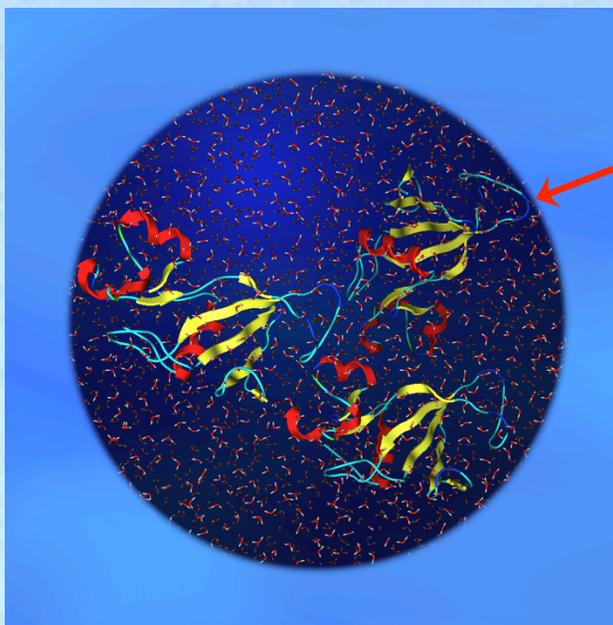
- **Strengths:** High efficiency and no artifacts from periodicity.
- **Weaknesses:** The information lost about molecular interactions at the molecular surface causes artifacts.



Explicit/Implicit Hybrid Model

The polymer and solvent inside the sphere are treated explicitly. Outside, the solvent is treated as a continuum dielectric medium.

- **Strengths:** Spherical geometry allows Poisson Boltzmann Eq. to be solved semi-analytically with no artifacts from periodicity.
- **Weaknesses:** Artifacts are caused by the discontinuous dielectric and molecular interactions at the spherical boundary, and there still remains a lot of explicit solvent.

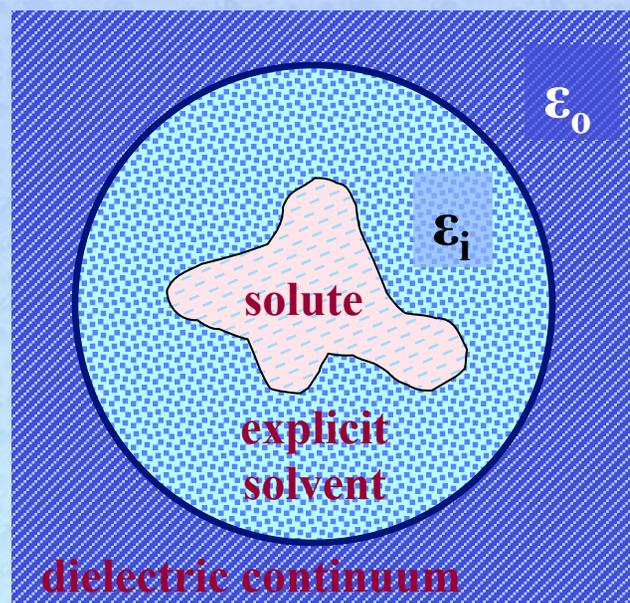


How close can we safely come to the spherical surface?

Reaction field from Poisson Equation

The total potential Φ inside the sphere equals the sum of the potentials due to all charges inside the sphere, and the potential due to the polarization of the solvent, called the **Reaction Field**.

$$\Phi_{\text{total}} = \Phi_{\text{inside}} + \Phi^{\text{RF}}$$



ϵ_i = dielectric constant
inside the sphere.

ϵ_0 = dielectric constant
outside the sphere.

Reaction field by direct expansion

The total potential Φ inside the sphere equals the sum of the potentials due to all charges inside the sphere, and the potential due to the polarization of the solvent, called the **Reaction Field**.

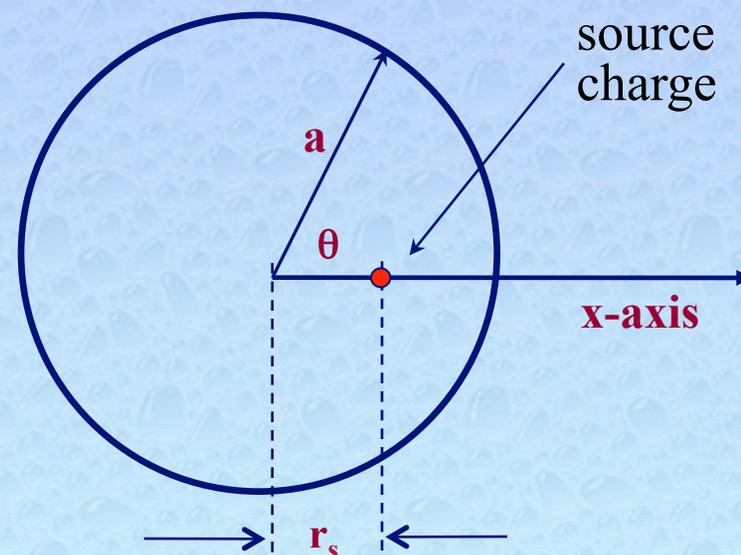
$$\Phi_{\text{total}} = \Phi_{\text{inside}} + \Phi^{\text{RF}}$$

For 1 source charge along the x-axis:

Due to azimuthal symmetry, the reaction potential $\Phi(r, \theta)$ can be expressed in terms of Legendre polynomials of $\cos(\theta)$:

$$\Phi^{\text{RF}}(r) = \sum_{n=0}^{\infty} B_n r^n P_n(\cos \theta), r \leq a,$$

$$B_n = \frac{q}{4\pi\epsilon_i} \cdot \frac{r_s^n}{a^{2n+1}} \cdot \gamma \cdot \left(1 + \frac{1+\gamma}{1-\gamma+2n} \right), \quad n \geq 0, \quad \gamma = \frac{\epsilon_i - \epsilon_o}{\epsilon_i + \epsilon_o}.$$



Reaction field from direct expansion

$$\Phi^{RF}(\mathbf{r}) = \frac{1}{4\pi\epsilon_i r_{kelvin}} \frac{\gamma q a}{r_s} \sum_{n=0}^{\infty} \left(\frac{r}{r_{kelvin}} \right)^n P_n(\cos\theta) + \frac{q}{4\pi\epsilon_i a} \frac{\gamma(1+\gamma)}{2} \sum_{n=0}^{\infty} \left(\frac{1}{r_{kelvin}} \right)^{\frac{1-\gamma}{2} + n} \frac{1}{\frac{1-\gamma}{2} + n} r^n P_n(\cos\theta)$$

Identify as the expansion of a point charge located outside the sphere after summing up the terms.

← same ID

$$\frac{q_{kelvin}}{4\pi\epsilon_i |r - r_{kelvin}|}$$

where

$$q_{kelvin} = \gamma a q / r_s$$

$$r_{kelvin} = \frac{a^2}{r_s}$$

where

$$q'(x) = \frac{q}{a} \frac{\gamma(1+\gamma)}{2} \left(\frac{x}{r_{kelvin}} \right)^{-\frac{1-\gamma}{2}}, \quad r_{kelvin} \leq x$$

trick

$$\left(\frac{1}{r_{kelvin}} \right)^{\frac{1-\gamma}{2} + n} \frac{1}{\frac{1-\gamma}{2} + n} = \int_{r_{kelvin}}^{\infty} \frac{1}{x^{\frac{1-\gamma}{2} + n + 1}} dx$$

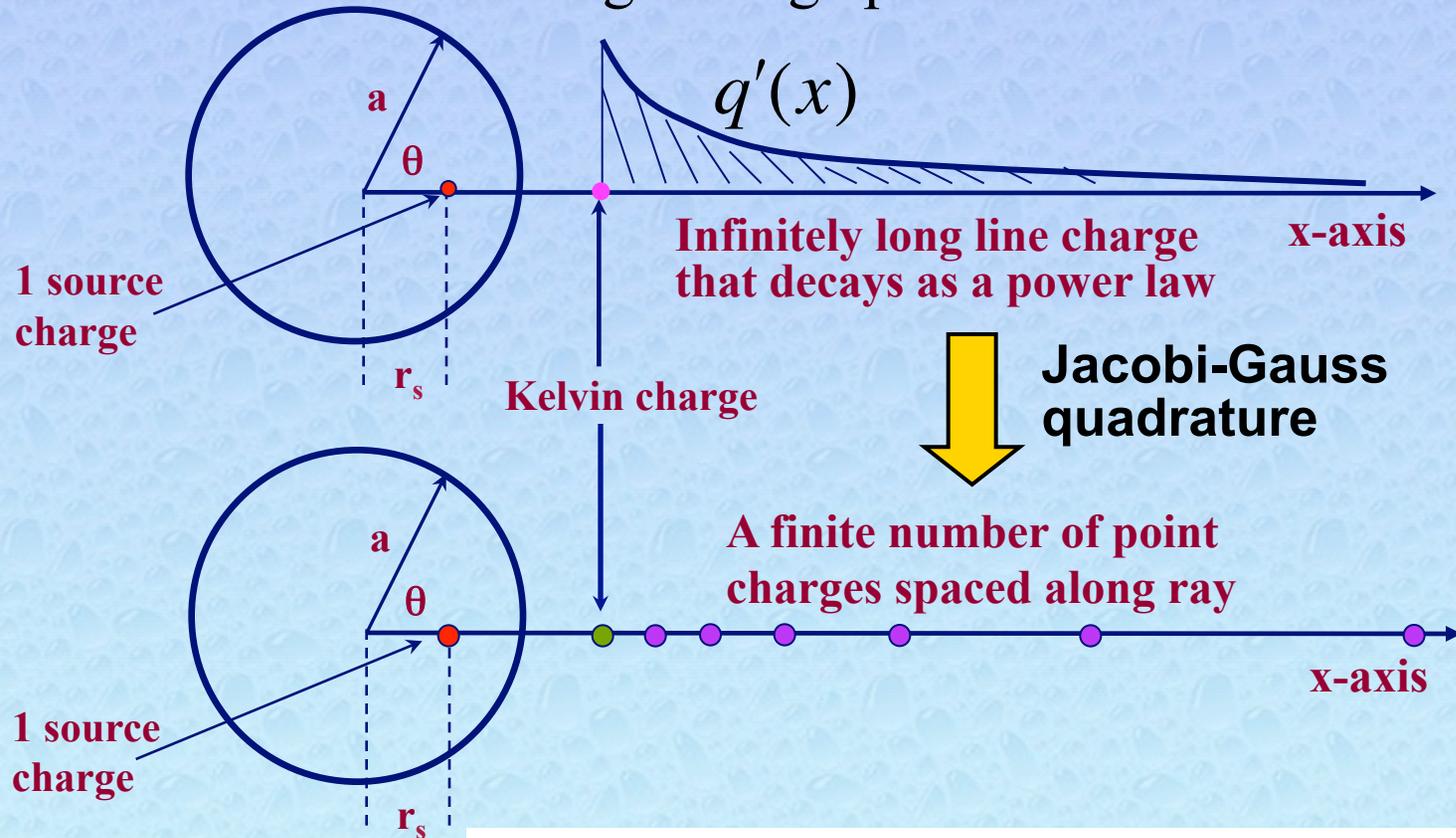
Plug back into Eq. and interchange integration with the summation.

$$\int_{r_{kelvin}}^{\infty} \left[\frac{q'(x)}{4\pi\epsilon_i x} \sum_{n=0}^{\infty} \left(\frac{r}{x} \right)^n P_n(\cos\theta) \right] dx$$

Reaction field from image charges

Result by C. Neumann (1883)

Reaction field = a Kelvin image charge plus an infinite line charge.



$$\Phi^{RF}(\mathbf{r}) \approx \frac{q_{\text{kelvin}}}{4\pi\epsilon_i |\mathbf{r} - \mathbf{r}_{\text{kelvin}}|} + \sum_{m=1}^M \frac{q'_m}{4\pi\epsilon_i |\mathbf{r} - \mathbf{x}_m|}$$

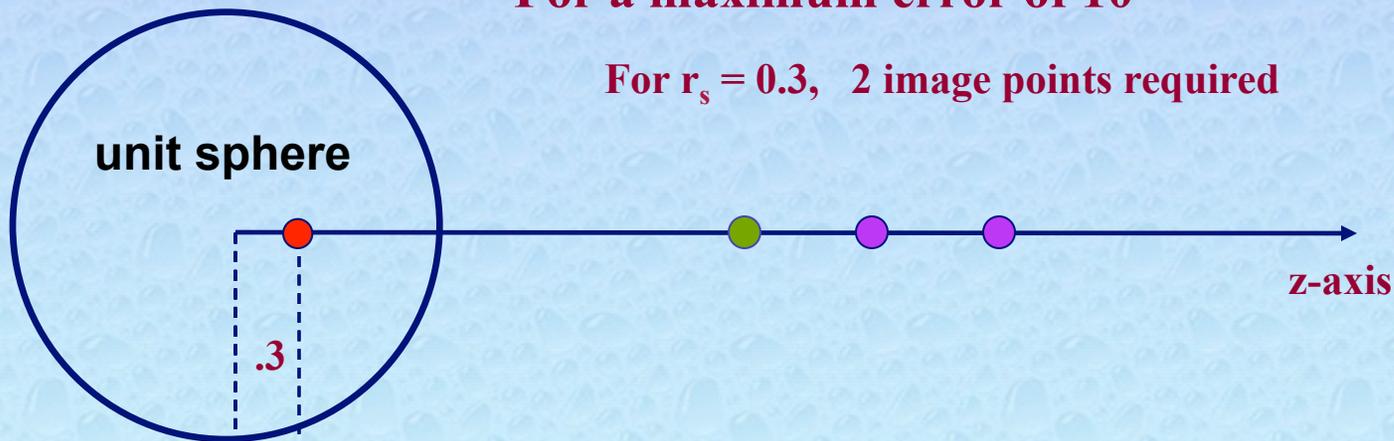
Reaction field from M+1 image charges

Numerical Problem: Replacing the integral over the line charge density with Jacobi - Gauss Quadrature involving M discrete points yields:

$$\Phi^{RF}(\mathbf{r}) \approx \frac{q_{\text{kelvin}}}{4\pi\epsilon_i |\mathbf{r} - \mathbf{r}_{\text{kelvin}}|} + \sum_{m=1}^M \frac{q'_m}{4\pi\epsilon_i |\mathbf{r} - \mathbf{x}_m|}$$

For a maximum error of 10^{-3}

For $r_s = 0.3$, 2 image points required



Physical interpretation: The reaction potential can be approximated by a Kelvin image charge and a finite number of additional point charges.

W. Cai, S. Deng and D. Jacobs, J. Comp. Phys. **223**:846-864 (2007)

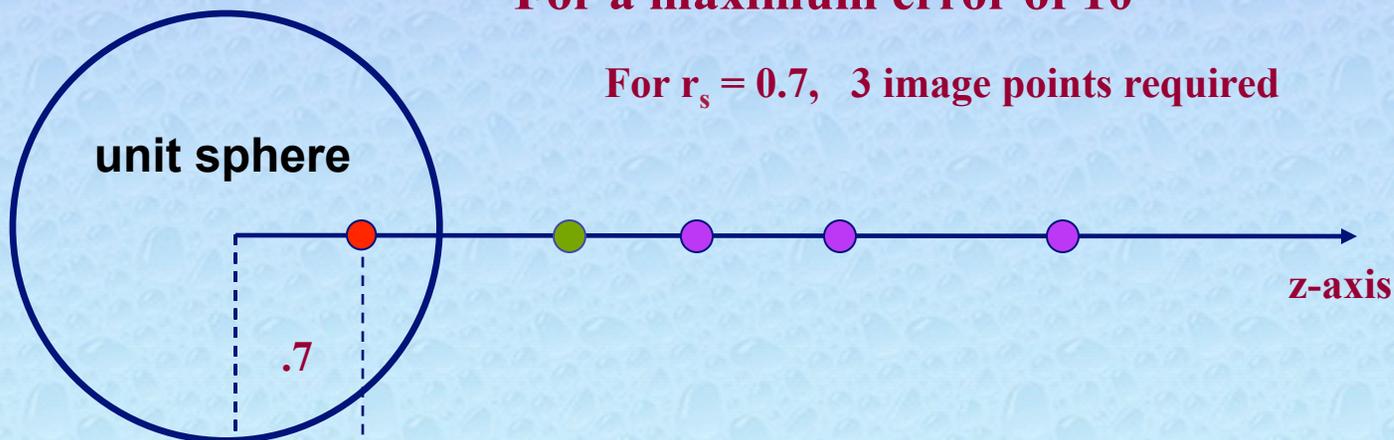
Reaction field from M+1 image charges

Numerical Problem: Replacing the integral over the line charge density with Jacobi - Gauss Quadrature involving M discrete points yields:

$$\Phi^{RF}(\mathbf{r}) \approx \frac{q_{\text{kelvin}}}{4\pi\epsilon_i |\mathbf{r} - \mathbf{r}_{\text{kelvin}}|} + \sum_{m=1}^M \frac{q'_m}{4\pi\epsilon_i |\mathbf{r} - \mathbf{x}_m|}$$

For a maximum error of 10^{-3}

For $r_s = 0.7$, 3 image points required



Physical interpretation: The reaction potential can be approximated by a Kelvin image charge and a finite number of additional point charges.

W. Cai, S. Deng and D. Jacobs, J. Comp. Phys. **223**:846-864 (2007)

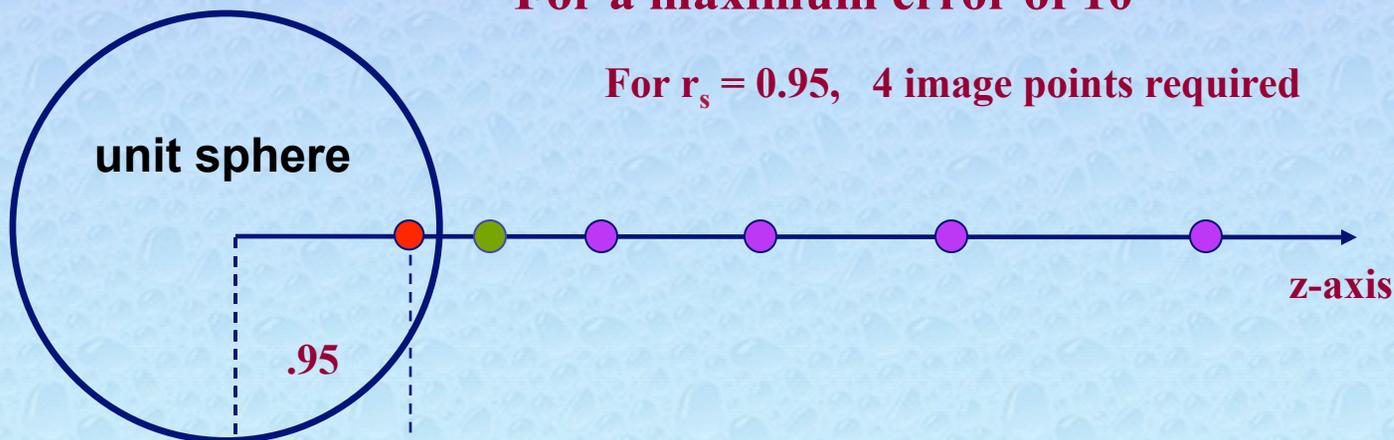
Reaction field from M+1 image charges

Numerical Problem: Replacing the integral over the line charge density with Jacobi - Gauss Quadrature involving M discrete points yields:

$$\Phi^{RF}(\mathbf{r}) \approx \frac{q_{\text{kelvin}}}{4\pi\epsilon_i |\mathbf{r} - \mathbf{r}_{\text{kelvin}}|} + \sum_{m=1}^M \frac{q'_m}{4\pi\epsilon_i |\mathbf{r} - \mathbf{x}_m|}$$

For a maximum error of 10^{-3}

For $r_s = 0.95$, 4 image points required



Physical interpretation: The reaction potential can be approximated by a Kelvin image charge and a finite number of additional point charges.

W. Cai, S. Deng and D. Jacobs, J. Comp. Phys. **223**:846-864 (2007)

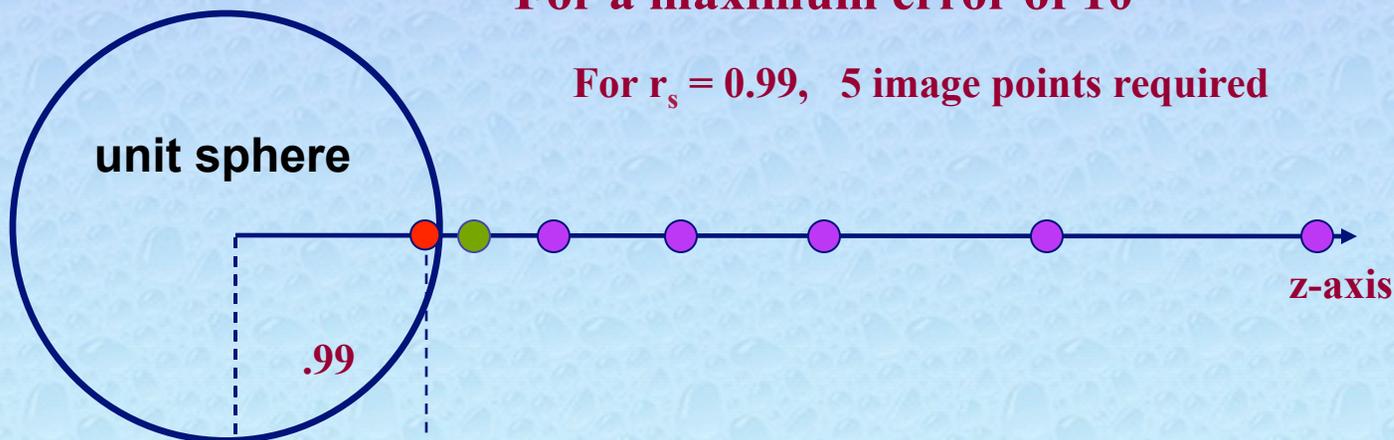
Reaction field from M+1 image charges

Numerical Problem: Replacing the integral over the line charge density with Jacobi - Gauss Quadrature involving M discrete points yields:

$$\Phi^{RF}(\mathbf{r}) \approx \frac{q_{\text{kelvin}}}{4\pi\epsilon_i |\mathbf{r} - \mathbf{r}_{\text{kelvin}}|} + \sum_{m=1}^M \frac{q'_m}{4\pi\epsilon_i |\mathbf{r} - \mathbf{x}_m|}$$

For a maximum error of 10^{-3}

For $r_s = 0.99$, 5 image points required

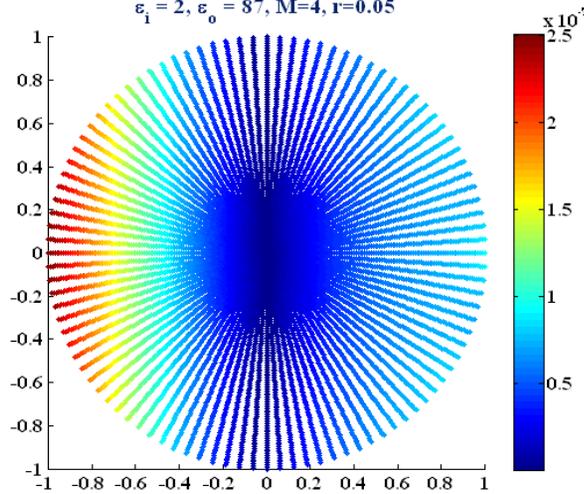


Physical interpretation: The reaction potential can be approximated by a Kelvin image charge and a finite number of additional point charges.

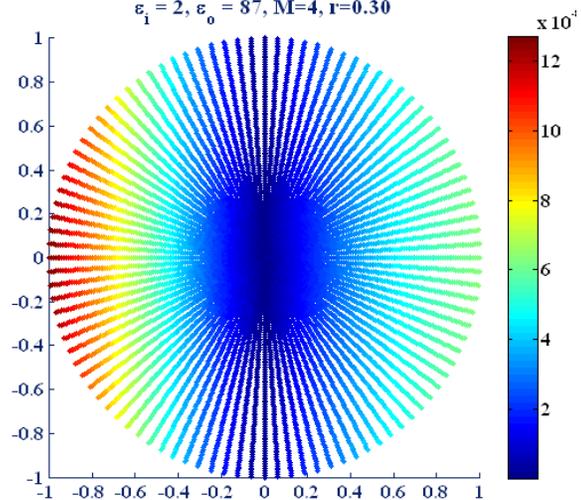
W. Cai, S. Deng and D. Jacobs, J. Comp. Phys. **223**:846-864 (2007)

Error distributions for 1 source charge

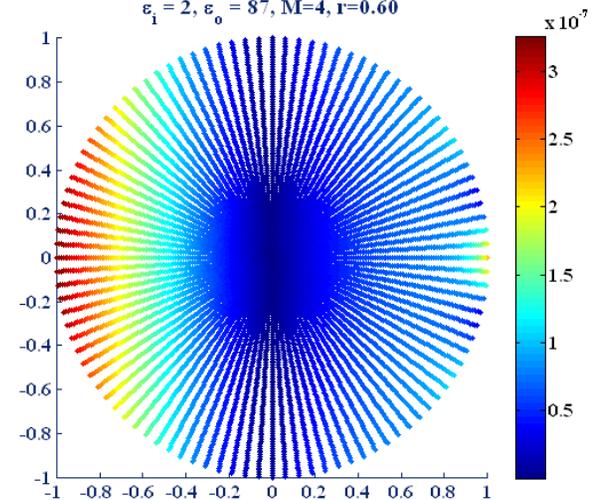
The Relative Error Distribution for
 $\epsilon_1 = 2, \epsilon_0 = 87, M=4, r=0.05$



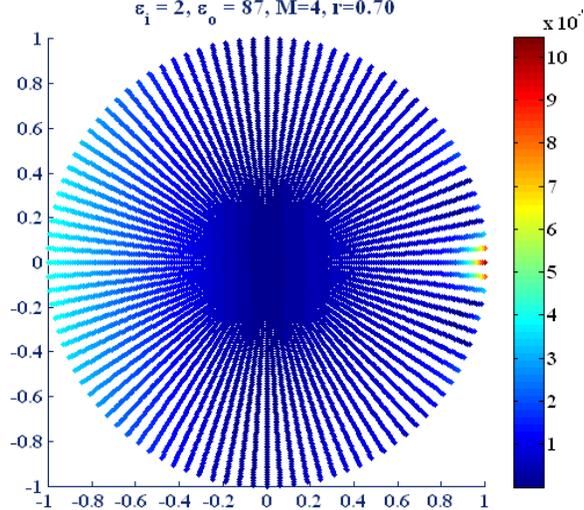
The Relative Error Distribution for
 $\epsilon_1 = 2, \epsilon_0 = 87, M=4, r=0.30$



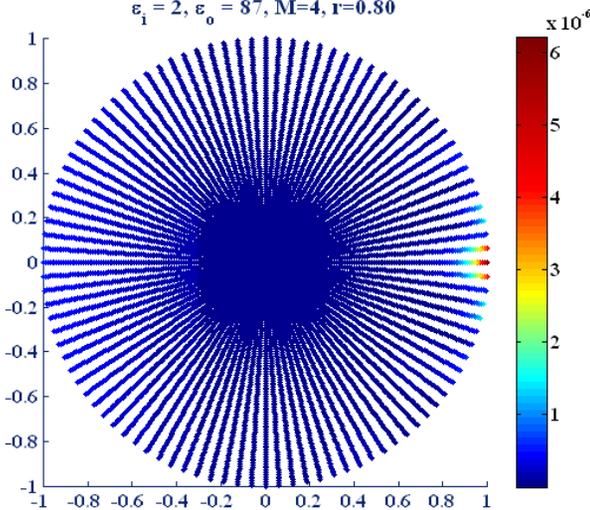
The Relative Error Distribution for
 $\epsilon_1 = 2, \epsilon_0 = 87, M=4, r=0.60$



The Relative Error Distribution for
 $\epsilon_1 = 2, \epsilon_0 = 87, M=4, r=0.70$

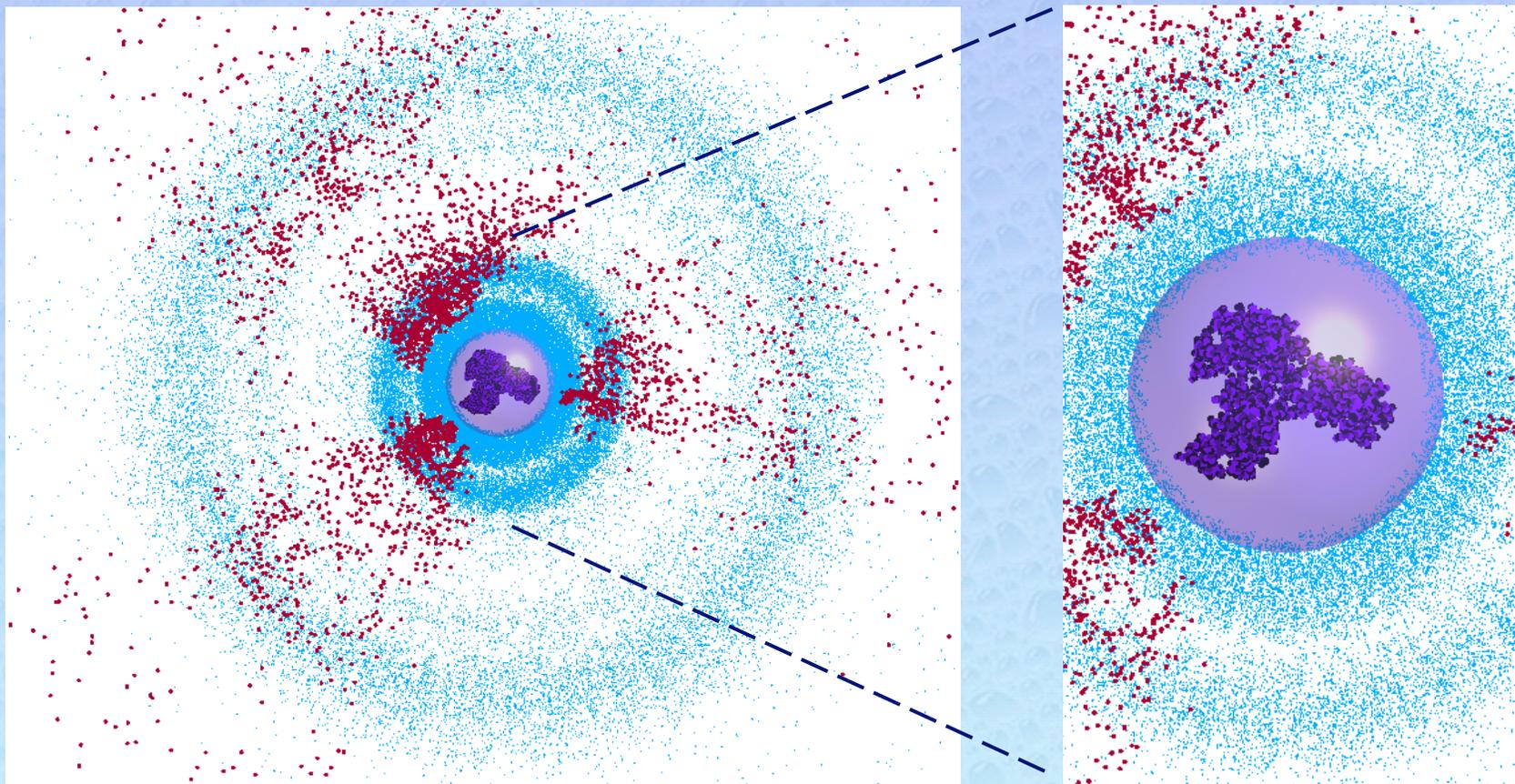


The Relative Error Distribution for
 $\epsilon_1 = 2, \epsilon_0 = 87, M=4, r=0.80$



The error distributions for one source charge at different positions away from the center of the unit circle.

Employing principle of superposition



Example: Protein 1BNI plus water molecules (not shown) and their images

- **Purple dots:** Partial charges on the protein
- **Red dots:** Image charges associated with the protein
- **Blue dots:** Image charges associated with explicit water molecules in the sphere

Setup for Molecular Dynamics Simulation

FEATURES

Simulation Box

truncated octahedron with periodic boundaries for short range forces.

Long range electrostatics

Fast Multipole Method (FMM)

Region I

production volume

Region II

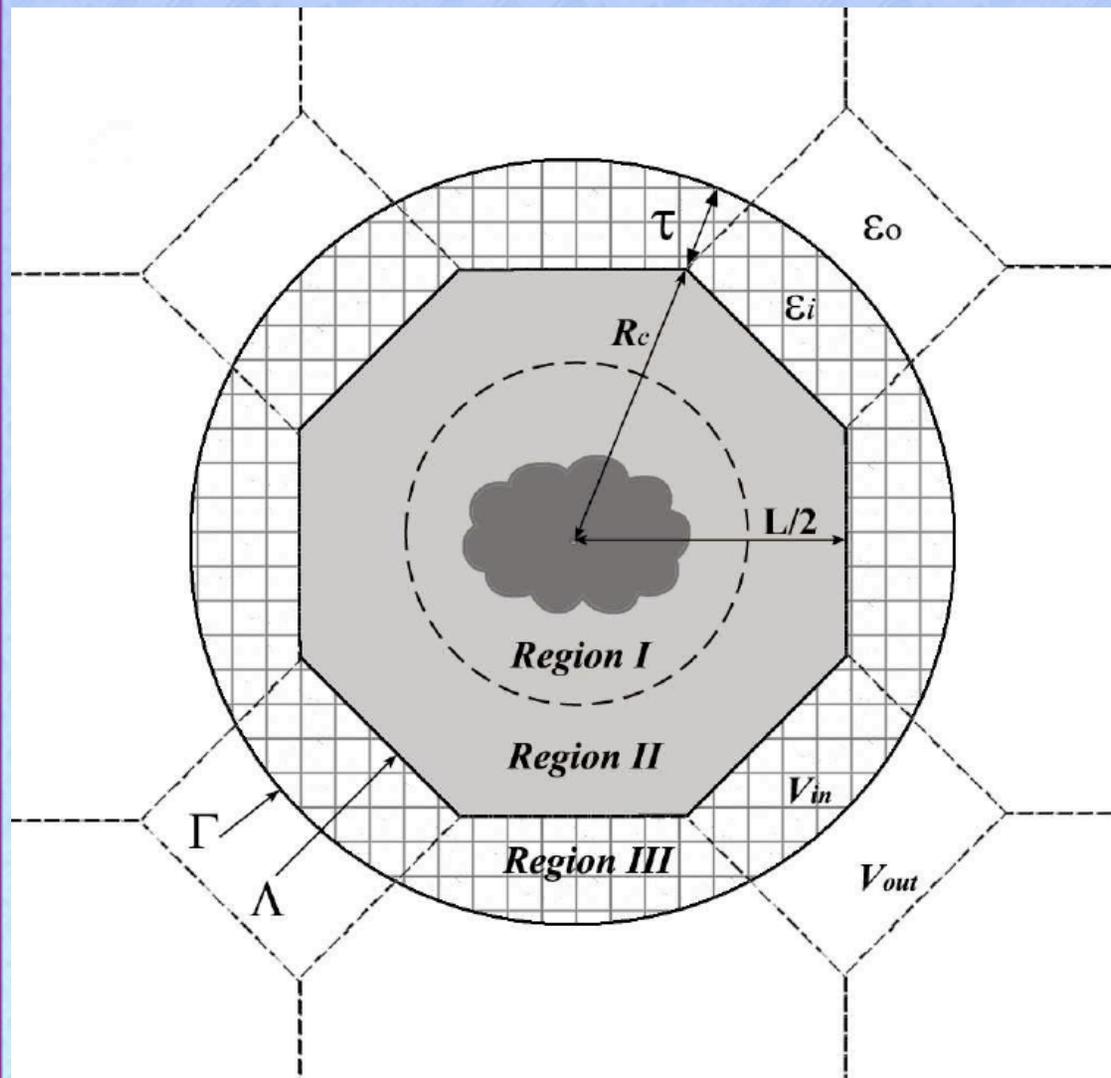
imaged water for Region III

Region III

buffer region required

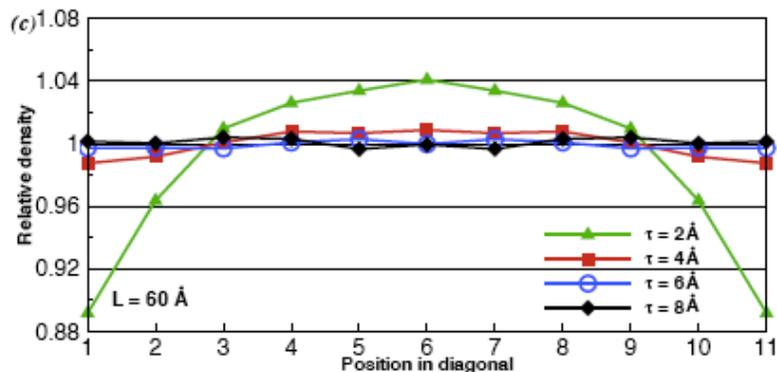
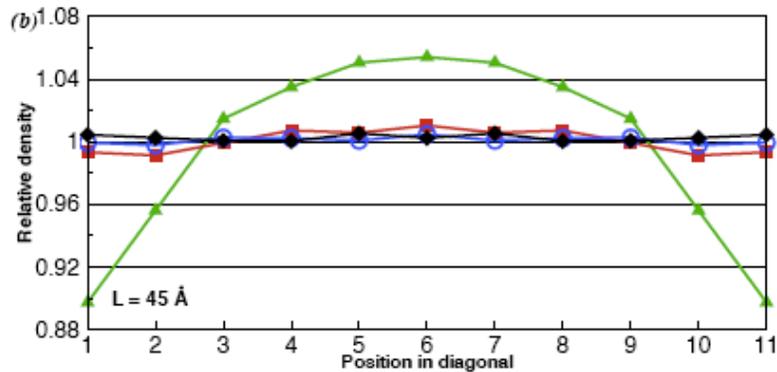
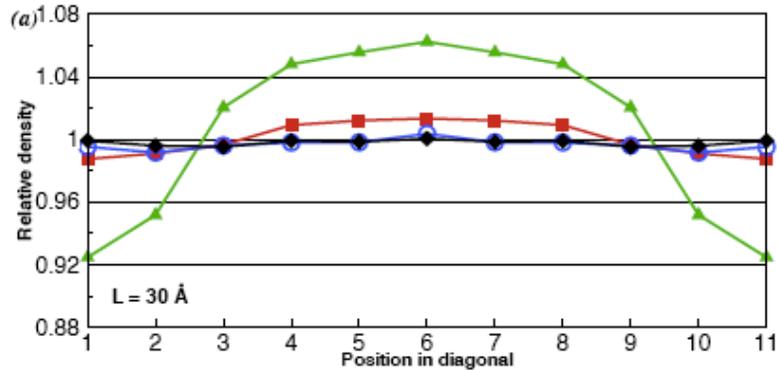
Bulk water simulation

Require structural and dynamic properties of water in the production volume to agree with PME calculations.



Y. Lin, A. Baumketner, S. Deng, Z. Xu, D. Jacobs, W. Cai, J. Chem. Phys. **131**:154103 (2009)

Results of Molecular Dynamics Simulation



Bulk properties of water are observed
Example: Density of water

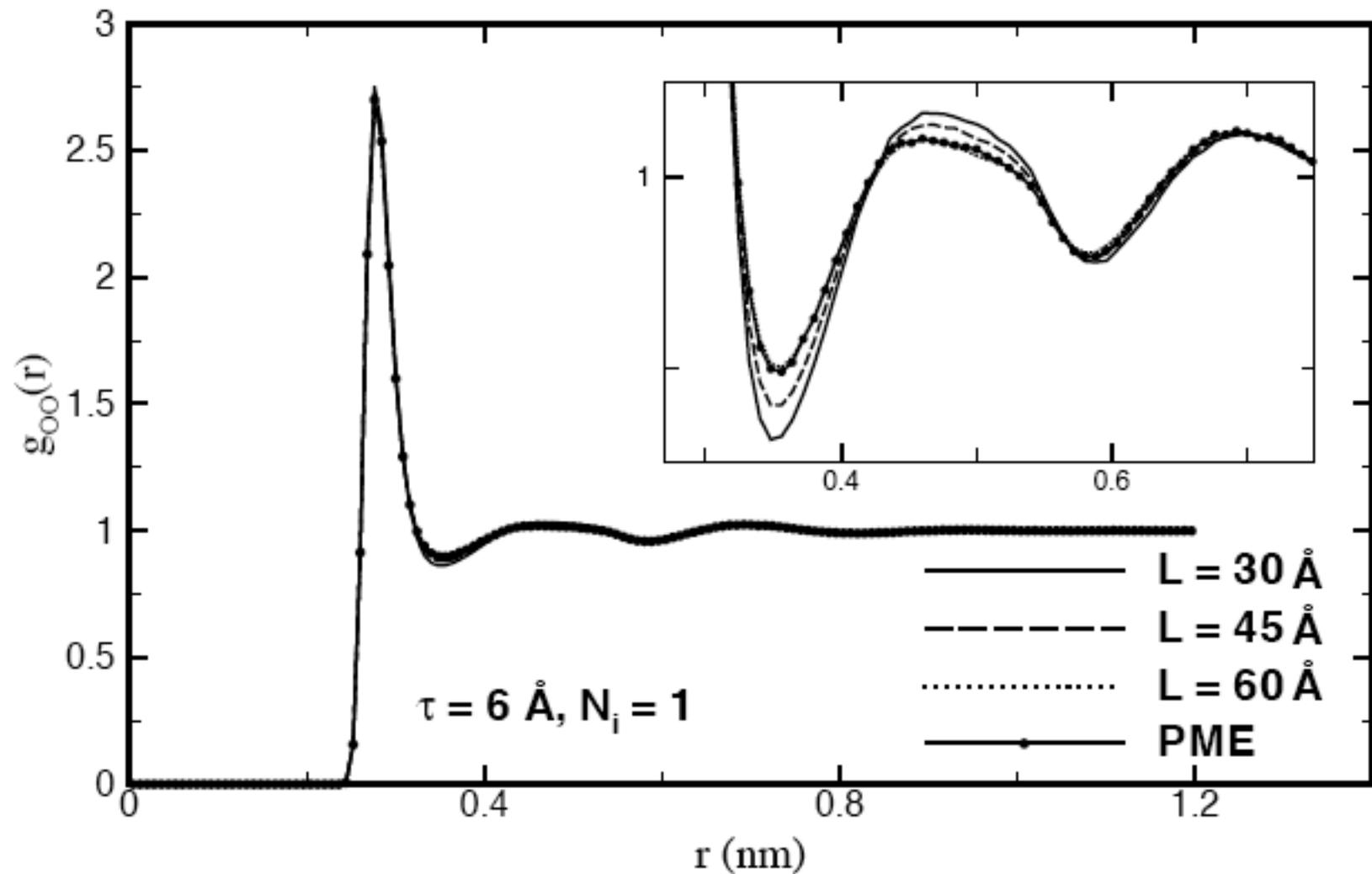
The density of water measured at 11 different bins along the diagonal of the TO-box is uniform in general, except for too small of a buffer region.

Finite size effects are small, but show up for small box size ($L=30$ Ang.) with small buffer region (4 Ang. or less).

Standard deviation in relative density

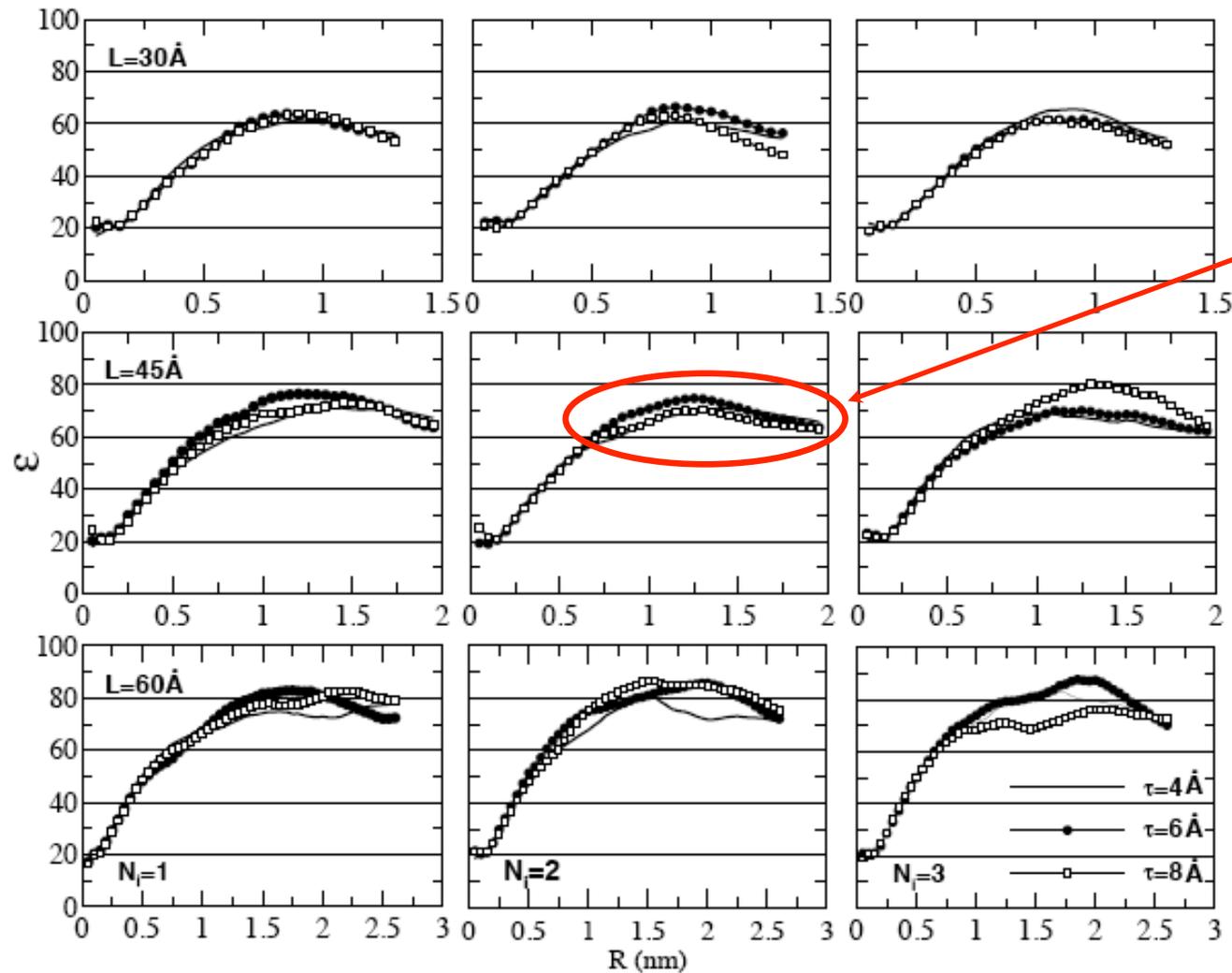
	$\tau=2 \text{ \AA}$	$\tau=4 \text{ \AA}$	$\tau=6 \text{ \AA}$	$\tau=8 \text{ \AA}$
$L=30 \text{ \AA}$	0.056	0.011	0.003	0.002
$L=45 \text{ \AA}$	0.060	0.007	0.002	0.002
$L=60 \text{ \AA}$	0.055	0.009	0.002	0.003

Results of Molecular Dynamics Simulation



Radial distribution function for oxygen-oxygen

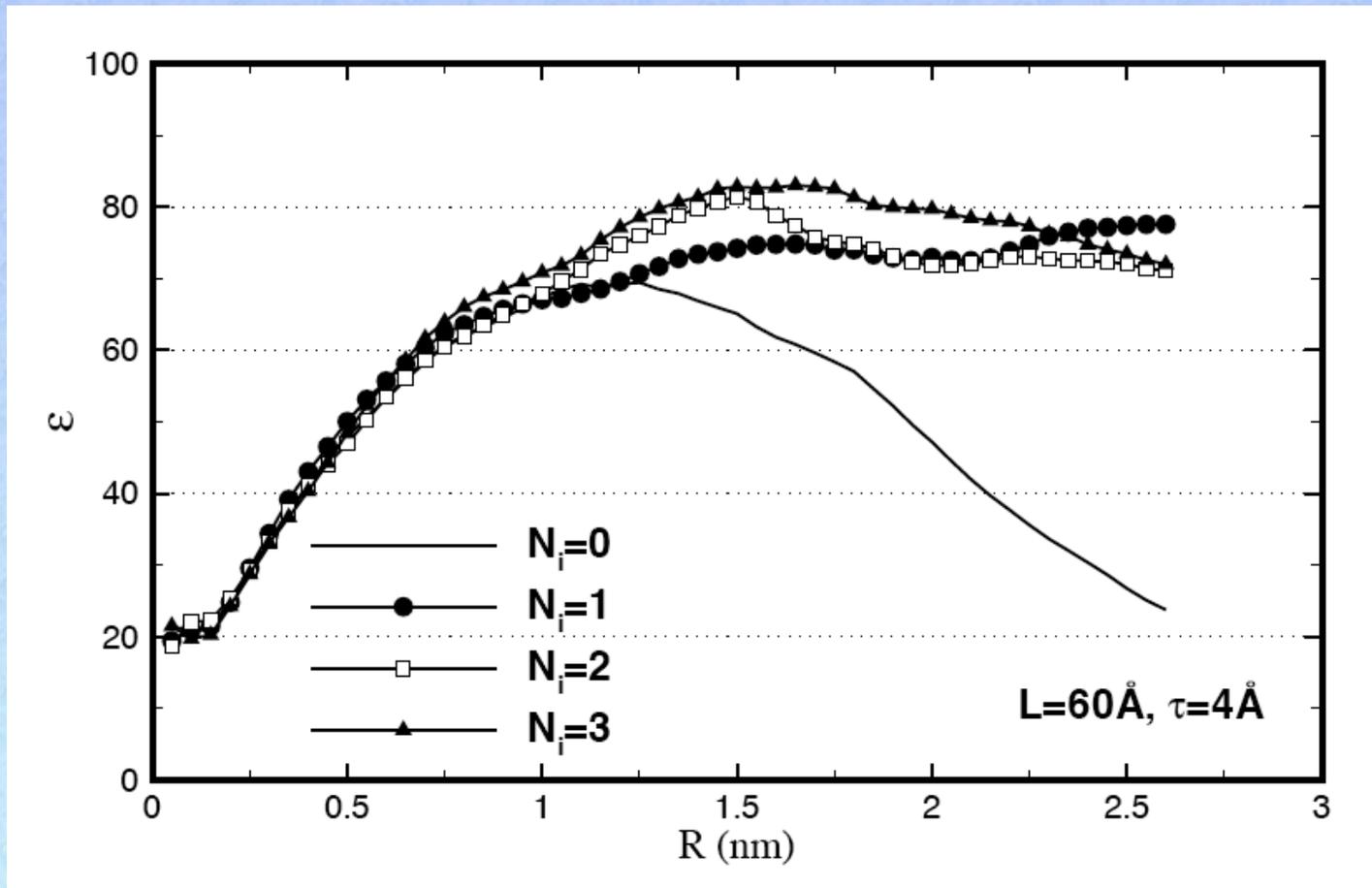
Results of Molecular Dynamics Simulation



The plateau values are approximately equal to the expected bulk value.

Dielectric constant calculated over a spherical ball of radius R .

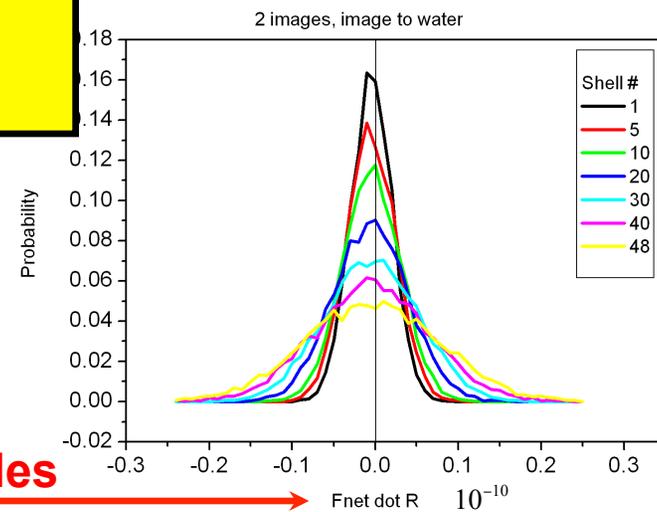
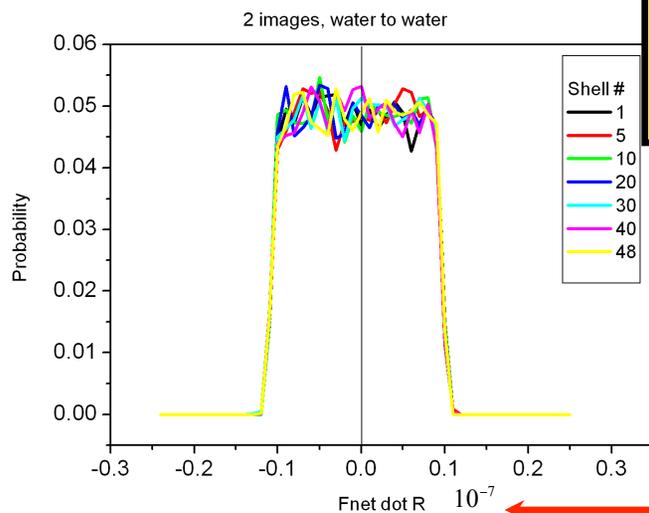
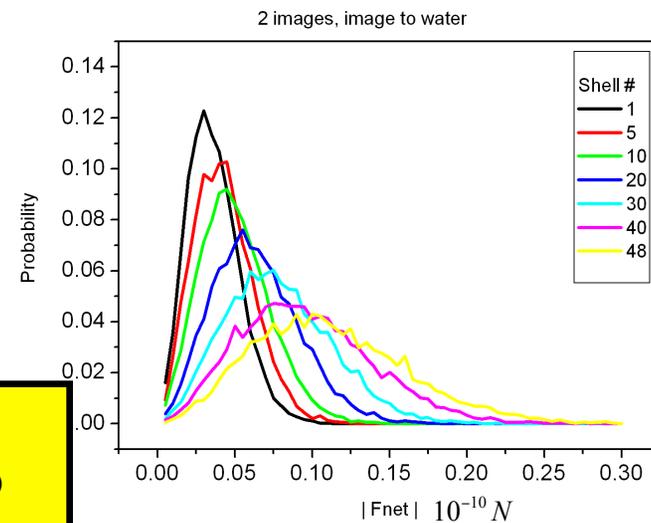
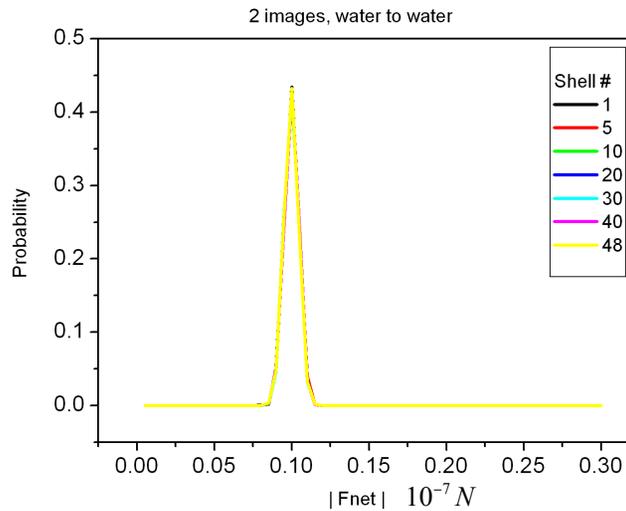
Results of Molecular Dynamics Simulation



Only one image charge (the Kelvin image) is sufficient to reproduce bulk water properties. **No image charge creates unphysical results.**

Results of Molecular Dynamics Simulation

Electrostatic force distributions

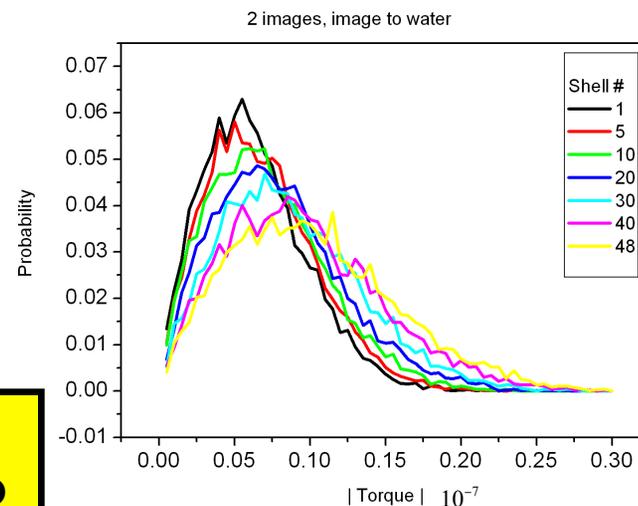
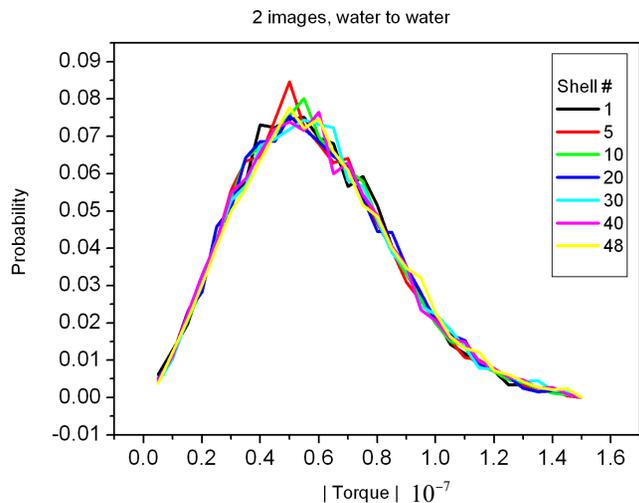


Electrostatic forces due to image charges have about a 1% effect.

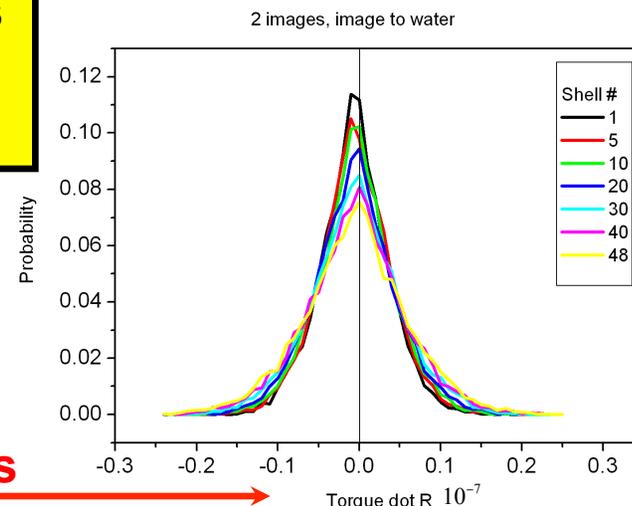
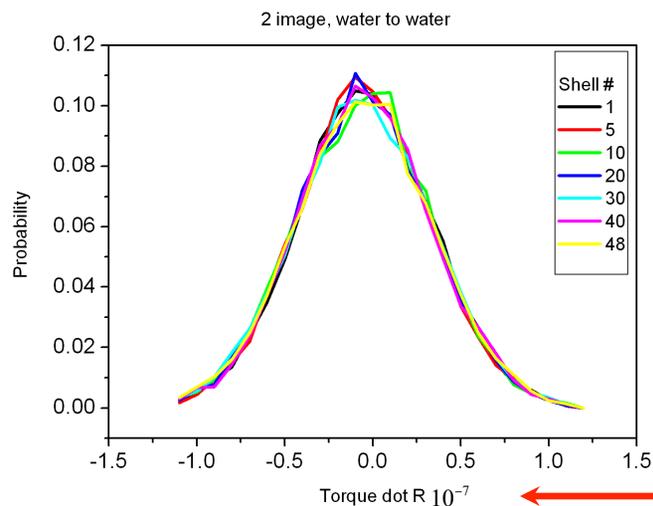
different scales

Results of Molecular Dynamics Simulation

Electrostatic torque distributions



Electrostatic torques due to image charges have about a 20% effect.



similar scales

Results of Molecular Dynamics Simulation

Free energy of Na⁺ solvation: Using a single ion

Estimates using the ICSM agree with previously published accurate estimates

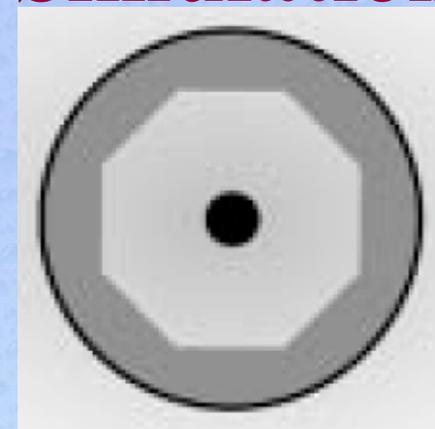


TABLE IV. Comparison of charging free energy ΔG_{cg}^s of sodium ion computed in this work by the ICSM and SSBP model (Ref. 70) with the values reported for systems of comparable dimensions by PME, straight cut-off method and finite-drop model (Ref. 49).

Method/model	ΔG_{cg}^s (kJ/mol)
ICSM (30 Å box)	-445
PME with <i>P</i> -type correction (Ref. 49) (31.3 Å box)	-420
Straight cut-off with $R_c = 14$ Å (Ref. 49) (31.3 Å box)	-442
Finite droplet (Ref. 49) (18 Å radius)	-429
SSBP (15 Å radius)	-388
Reference value (Ref. 49)	-480

Not accounting for finite size effects

best estimate

⁴⁹M.A. Kastholz and P.H. Huenenberger. J. Chem. Phys. 124, 224501 (2006)

Y. Lin, A. Baumketner, W. Song, S. Deng, D. Jacobs, W. Cai, J. Chem. Phys. 134:044105 (2011)

Results of Molecular Dynamics Simulation

Free energy of Na⁺ solvation: Using a single ion

Estimates using the ICSM agree with previously published accurate estimates

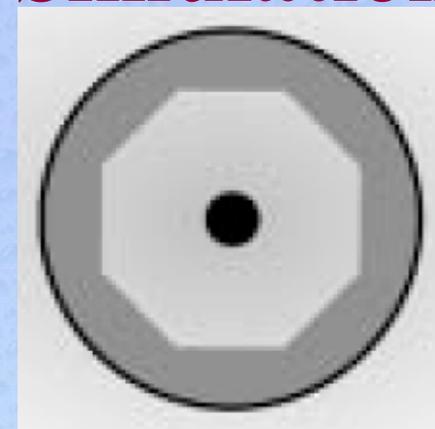


TABLE I. Electrostatic solvation energy ΔG_{cg} (in kJ/mol) of a sodium ion in water obtained in this work in simulation boxes of different sizes L . Finite-size corrections ΔG_c are evaluated separately from the charging free energy ΔG_{cg}^s computed directly in the simulations (explained in the text).

L (Å)	ΔG_{cg}^s	ΔG_c	ΔG_{cg}
30	-445	-64	-509
45	-457	-33	-490
60	-465	-20	-485

Accounting for finite size effects tends to -480 in a systematic way.

Y. Lin, A. Baumketner, W. Song, S. Deng, D. Jacobs, W. Cai, J. Chem. Phys. **134**:044105 (2011)

Results of Molecular Dynamics Simulation

Free energy of Na⁺ solvation: Using a single ion

Estimates using the ICSM agree with previously published accurate estimates

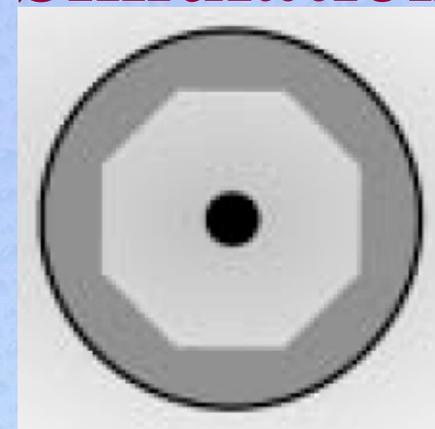


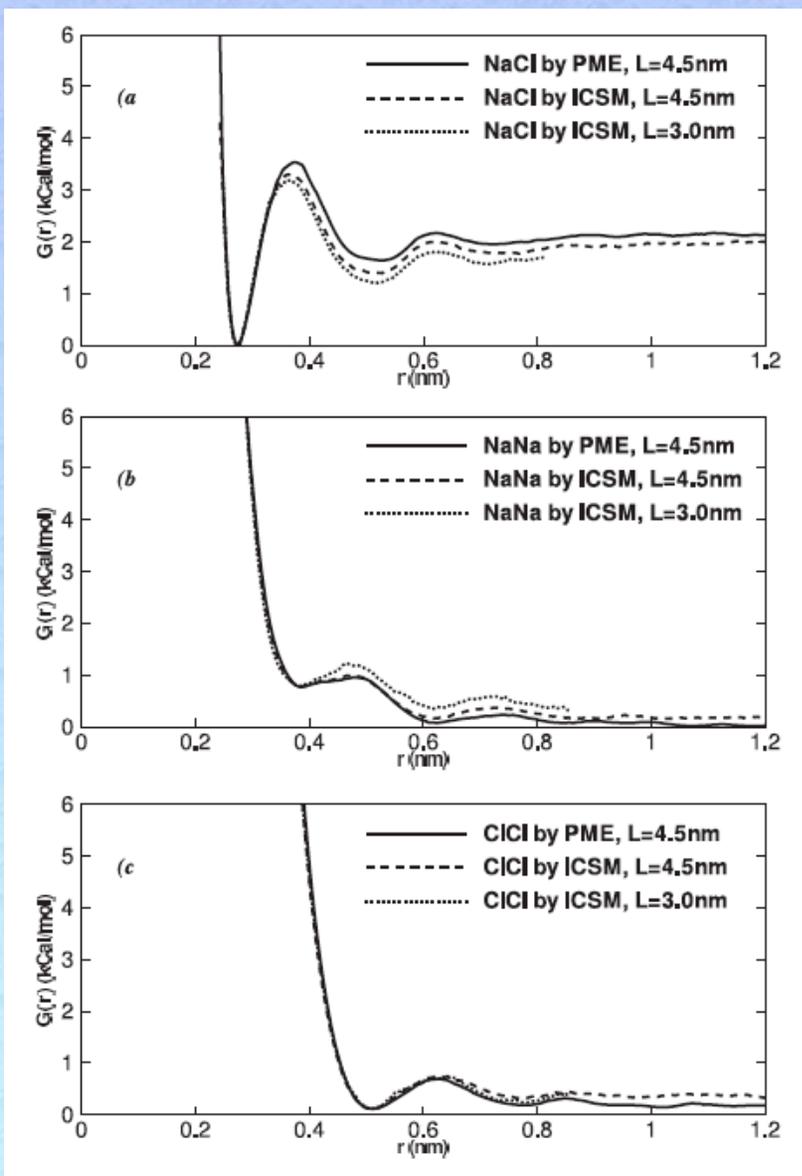
TABLE II. Charging free energy ΔG_{cg}^s computed for different ion locations in the 60 Å simulation box.

Distance to origin (Å)	ΔG_{cg}^s (kJ/mol)
0	-465
6.0	-468
12.0	-467
18.0	-468
24.0	-459

No systematic dependence on position of ion in the TO-box.

Y. Lin, A. Baumketner, W. Song, S. Deng, D. Jacobs, W. Cai, J. Chem. Phys. **134**:044105 (2011)

Results of Molecular Dynamics Simulation



Potential of Mean Force (PMF) for ion pairs

Results using ICSM agree with previously published accurate results.

Y. Lin, et. al., J. Chem. Phys. **134**:044105 (2011)

Improved image charge formulas

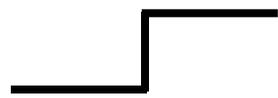
Build in a transition layer?

Dielectric Profile:

$$\epsilon(r) = \begin{cases} \epsilon_{in} & \text{for } r \leq a \\ \epsilon_p(r) & \text{for } a \leq r < b \\ \epsilon_{out} & \text{for } r \geq b \end{cases}$$

Step Function:

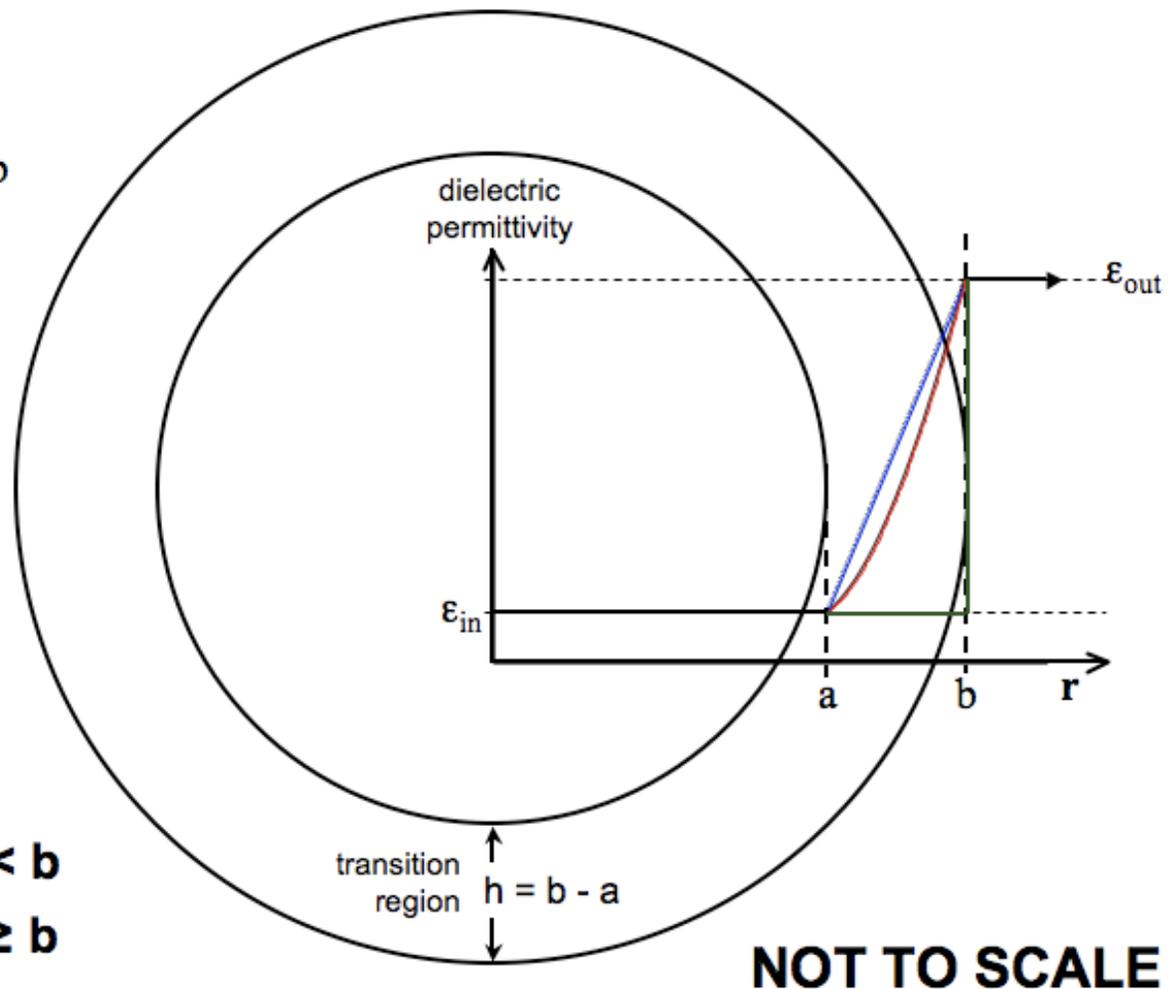
$$\epsilon_p(r) = \epsilon_{in}$$



**Discontinuous
Dielectric Model
(DDM)**

Explicit solvent: $r < b$

Implicit solvent: $r \geq b$

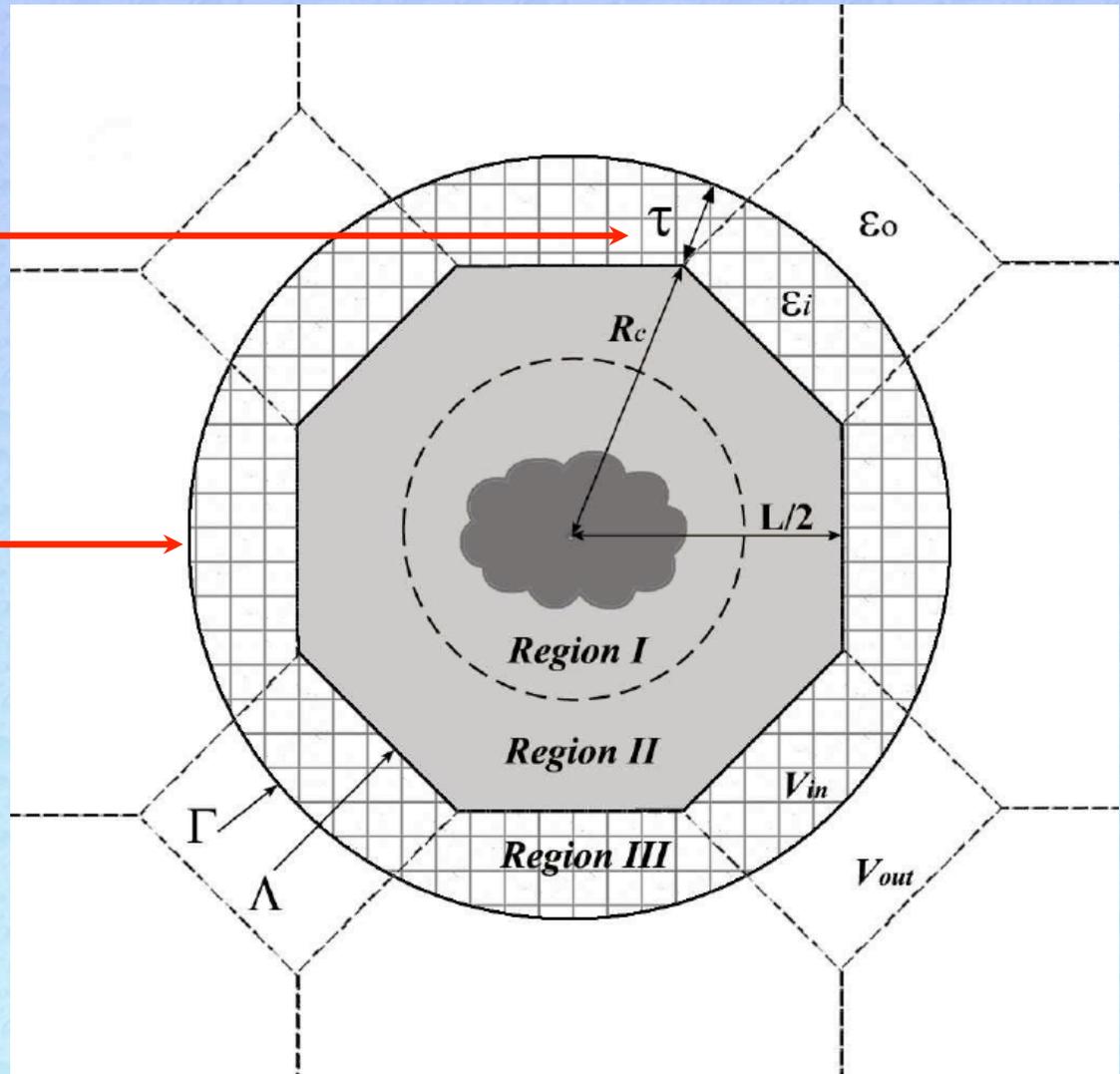


Improved image charge formulas

Two motivations

Reduce buffer region

Reduce artifacts on the reaction field caused by the DDM



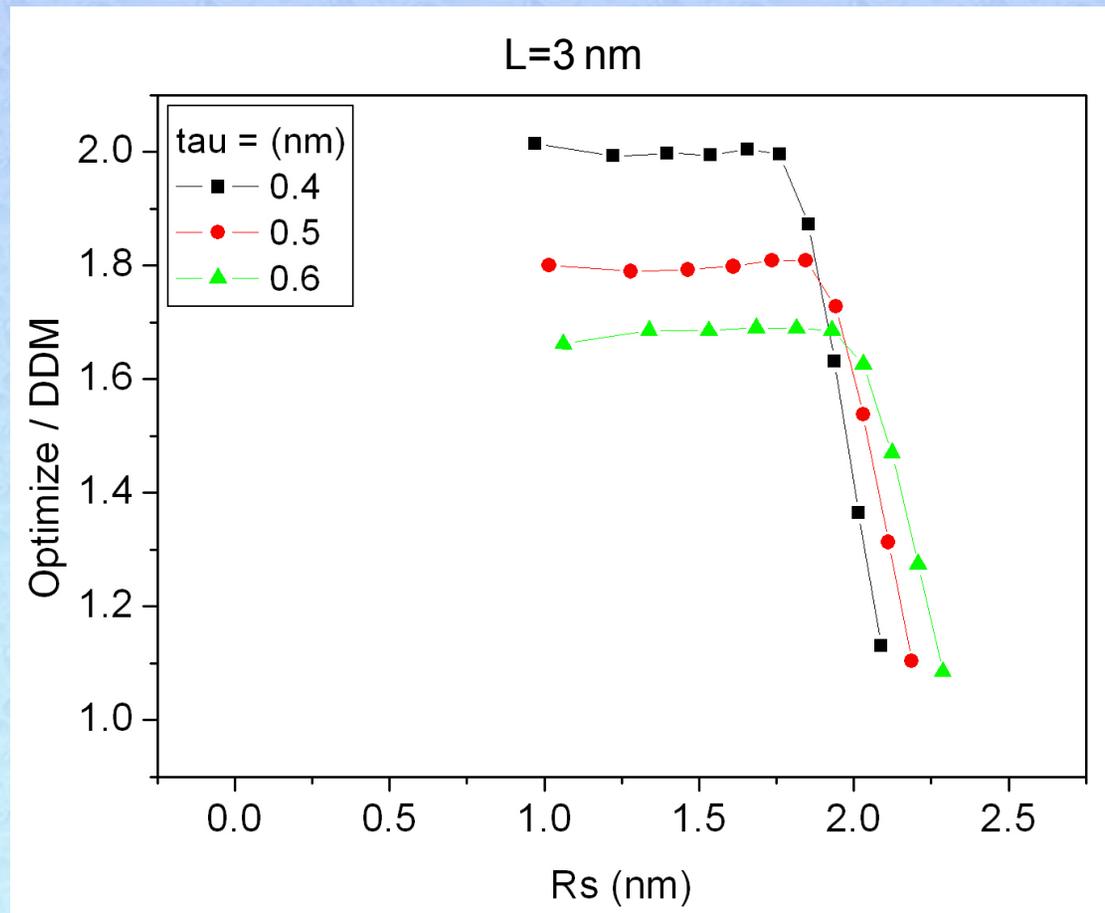
Improved image charge formulas

preliminary results

See poster by Wei Song

Optimized image charges for reaction field calculations

Ratio of optimized image charge to that of the DDM as a function of source charge location.



Conclusions

- Our results on bulk water simulations and ion charging free energies suggest the **Image Charge Solvation Model (ICSM)** provides a high accuracy calculation for the reaction field while minimizing finite size effects during the molecular dynamics simulation.
- The reaction field is weak compared to direct local interactions with about a 1% effect on atomic forces, but it is critical to get local structure of water correct due to torques on molecular orientations where there is about a 20% effect.
- The ICSM can be generalized to ionic solutions. More will be said about image charge methods by **Wei Cai** in his talk on *Image Approximations to Reaction Fields in Inhomogeneous Media* this afternoon.
- The ICSM is implemented in TINKER. Preliminary benchmarks show that the crossover point for ICSM to be faster than PME is a TO-box size of 80 Angstroms corresponding to about 25,000 atoms.