Developing Monovalent Ion Parameters for the Optimal Point Charge (OPC) Water Model

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What are MD simulations?

- Model and predict the structure and dynamics of large macromolecules.
- Force field equation implemented in AMBER

\[
V = \sum_{i}^{n_{\text{bonds}}} b_i (r_i - r_{i,eq})^2 + \sum_{i}^{n_{\text{angles}}} a_i (\theta_i - \theta_{i,eq})^2 \\
+ \sum_{i}^{n_{\text{dihedral}}} \sum_{n}^{n_{\text{max}}} V_{i,n}/2 [1 + \cos(n\varphi_i - \gamma_{i,n})] \\
+ \sum_{i<j}^{n_{\text{atoms}}} \varepsilon_{ij} \left[ \left( \frac{R_{\text{min},ij}}{r_{ij}} \right)^{12} - 2 \left( \frac{R_{\text{min},ij}}{r_{ij}} \right)^{6} \right] + \sum_{i<j}^{n_{\text{atoms}}} \frac{q_i q_j}{4\pi\varepsilon_0 r_{ij}}
\]
What are Water Models?

<table>
<thead>
<tr>
<th>Model</th>
<th>O</th>
<th>H₁</th>
<th>H₂</th>
<th>EP₁</th>
<th>EP₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 point</td>
<td>Mass Charge</td>
<td>Mass Charge</td>
<td>Mass Charge</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>vDW</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 point</td>
<td>Mass vDW</td>
<td>Mass Charge</td>
<td>Mass Charge</td>
<td>Charge</td>
<td></td>
</tr>
<tr>
<td>5 point</td>
<td>Mass vDW</td>
<td>Mass Charge</td>
<td>Mass Charge</td>
<td>Charge</td>
<td>Charge</td>
</tr>
</tbody>
</table>

3 point model i.e. TIP3P and SPC

4 point model i.e. TIP4P-Ew and OPC

5 point model i.e. TIP5P
What is OPC?

- Optimal point charge (OPC)
  - Saeed Izadi, Ramu Anandakrishnan and Alexey V. Onufriev, Published 2014
  - Derived to reproduce quantum mechanical electrostatic potential
  - Simulates the bulk properties of water better than other models

What are ion parameters?

\[ V = \sum_{i}^{n_{\text{bonds}}} b_i (r_{i,eq} - r_i)^2 + \sum_{i}^{n_{\text{angles}}} a_i (\theta_{i,eq} - \theta_i)^2 + \sum_{i}^{n_{\text{dihedral}}} \sum_{j}^{n_{\text{max}}} V_{i,n} \cos(n\varphi_i - \gamma_{i,n}) \]

\[ \sum_{i,j}^{n_{\text{atoms}}} \varepsilon_{ij} \left[ \left( \frac{R_{\text{min},ij}}{r_{ij}} \right)^{12} - 2 \left( \frac{R_{\text{min},ij}}{r_{ij}} \right)^{6} \right] \]

\[ \sum_{i,j}^{n_{\text{atoms}}} \frac{q_i q_j}{4\pi\varepsilon_0 r_{ij}} \]
What are Ion Parameters?

- Ions must be parameterized in order to provide coefficients for energy calculations in AMBER.

- Two parameters must be created for each ion, $\varepsilon$ and $R_{\text{min}}/2$.

- Lennard-Jones (LJ) potential has a well depth of $\varepsilon$ at a distance of $R_{\text{min}}$. 

\[ E_{\text{LJ}} = \varepsilon_{ij} \left[ \left( \frac{R_{\text{min},ij}}{r_{ij}} \right)^{12} - 2 \left( \frac{R_{\text{min},ij}}{r_{ij}} \right)^{6} \right] \]
How are Ion Parameters Developed?

- Most ion parameters are developed empirically.
- Parameters are chosen that produce the most realistic test results.
- In Suk Joung and Tomas E. Cheatham
  - TIP3P, SPC, and TIP4P-Ew ion parameters
- Kasper P. Jenson and William L. Jorgenson
  - SPC and TIP3P ion parameters
Lattice Constants (LC’s)

- The lattice constant is the spacing between unit cells.
- For FCC crystals this value is twice the interionic distance.
Lattice Constants

\[ \text{LE (kcal/mol)} \]

\[ \text{LC (Å)} \]

\[
\begin{array}{c|c|c|c|c|c|c|c|c|c}
5.0 & 5.5 & 6.0 & 6.5 & 7.0 & 7.5 & 8.0 & 8.5 & 9.0 \\
-5.0 & -4.8 & -4.6 & -4.4 & -4.2 & -4.0 & -3.8 & -3.6 & -3.4 \\
\end{array}
\]

\[
\begin{array}{c|c|c|c|c|c|c|c|c|c}
5.5 & 5.6 & 5.7 & 5.8 & 5.9 & 6.0 \\
-4.9 & -4.88 & -4.86 & -4.84 & -4.82 & -4.80 \\
\end{array}
\]

\[
\begin{array}{c|c|c|c|c|c|c|c|c|c}
\text{Na}^+ & \text{R}_{\text{min}}/2 = 1.369 Å \\
\text{Cl}^- & \text{R}_{\text{min}}/2 = 2.513 Å \\
\end{array}
\]
Hydration Free Energy

- Gives the energy from the interactions of the ion with water.
- Produced by slowly bringing the charges and Van der Waals to zero (thermodynamic integration).

$$\Delta G_{Hyd} = \int_0^1 \left( \frac{\partial V}{\partial \lambda} \right) d\lambda$$
Thermodynamic Integration (TI)

- TI is performed in two steps, charge elimination and Van der Waals (vdW) elimination
- Various intermediate states are produced (\( \lambda \)) and fit to a curve for each step
- The curve is integrated for each step and the two areas are added to produce a hydration free energy

\[
\partial V / \partial \lambda = \begin{cases} 
200 & \text{Charge} \\
4 & \text{vdW} 
\end{cases}
\]

\[
90.96 + 0.2360 = 91.20 \text{ kcal/mol}
\]
Radial Distribution Functions
Radial Distribution Functions

- Show the density of the oxygen atom in water with respect to radius from the ion.
- The ion-oxygen distance of the first peak is characteristic for each ion.

![Graph showing frequency of O atoms versus distance in Å](image-url)
Experimental Comparison

- Lattice Constants

- Hydration Free Energy

- Radial Distribution Function

\[ \Delta G_{Hyd} = \int_{0}^{1} \left( \frac{\partial V}{\partial \lambda} \right) d\lambda \]
Convergence Test

Run a large number of LC simulations for different $R_{\text{min}}$, $R_{\text{min}}$ pairs for NaCl, KCl, LiCl, ....

Pick $R_{\text{min}}$'s that minimize error in LC for each crystal

Collect Parameters

Run TI & RDF simulations for a variety of $R_{\text{min}}$, $\varepsilon$

Pick $\varepsilon$'s that minimize error in RDF & TI for each crystal

Run Test Simulations
Convergence Test

Run a large number of LC simulations for different $R_{\text{min}}$, $R_{\text{min}}$ pairs for NaCl KCl LiCl, ....

Pick $R_{\text{min}}$’s that minimize error in LC for each crystal

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Pick $R_{\text{min}}$’s that minimize error in LC for each crystal

Pick $\varepsilon$’s that minimize error in RDF & TI for each crystal

- LiF
- LiCl
- LiBr
- NaF
- NaCl
- NaBr
- KF
- KCl
- KBr

Run Test Simulations
Lattice Calculations

- Involve no “simulation” only energy evaluation so list is short
- Particle mesh Ewald
- Non-bonded cutoff
- Total system size
Non-bonded Cutoff
Lattice Calculations

- Particle Mesh Ewald (Default Settings OK)
- Non-bonded Cutoff (12Å)
- Total System Size (No dependence)
TI convergence testing

- Electrostatics play a big role
- Computation is more expensive
- NTWX
- Equilibration Time
- Buffer Size
- Production Time
- Number of λ values
- Non bonded Cutoff
Buffer Size/Production Time

Hydration Free Energy vs. Time (s)
TI Convergence Testing

- NTWX (50ps)
- Equilibration Time (2ns)
- Buffer Size (in process)
- Production Time (in process)
- Number of λ Values (3 for testing, 9 for production more work for vdw)
- Non-Bonded Cutoff (last step)
RDF Convergence Testing

- Equilibration time
- Sampling time
- Period between samples
- Size of the periodic box
Equilibration Time

<table>
<thead>
<tr>
<th>First 10ns</th>
<th>Middle 10ns</th>
<th>Last 10ns</th>
<th>STDEV</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.483852</td>
<td>2.483645</td>
<td>2.483822</td>
<td>0.000112</td>
<td>.000207</td>
</tr>
</tbody>
</table>

- Density of O vs. R (Å) for First 10ns, Middle 10ns, and Last 10ns.
Sampling Time

<table>
<thead>
<tr>
<th>Sampling Time</th>
<th>Density of O (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1ns</td>
<td>2.481208</td>
</tr>
<tr>
<td>2ns</td>
<td>2.483100</td>
</tr>
<tr>
<td>5ns</td>
<td>2.483755</td>
</tr>
<tr>
<td>10ns</td>
<td>2.483822</td>
</tr>
<tr>
<td>STDEV</td>
<td>0.001219</td>
</tr>
<tr>
<td>Range</td>
<td>0.002614</td>
</tr>
</tbody>
</table>
Buffer Size

Na⁺ RDF

- 14.3 Buffer
- 16 Buffer
- 18 Buffer
- 20 Buffer
- 25 Buffer

Density of O

Density of O

Ion-Oxygen Distance (Å)

Buffer Size (Å)
RDF Convergence Testing

- Equilibration time (520ps minimum; 100ns used)
- Sampling time (10ns)
- Period between samples (500fs)
- Size of the periodic box (15Å buffer zone → 26Å truncated octahedron)
Convergence Test

Run a large number of LC simulations for different $R_{\text{min}}$, $R_{\text{min}}$ pairs for NaCl KCl LiCl....

Pick $R_{\text{min}}$'s that minimize error in LC for each crystal

Run TI & RDF simulations for a variety of $R_{\text{min}}$, $\epsilon$

Pick $\epsilon$'s that minimize error in RDF & TI for each crystal

Collect Parameters

Run Test Simulations
RDF surfaces

Chose values about ±15% relative to TIP4P-Ew parameters by Joung and Cheatham

\[
\begin{align*}
\text{Na}^+ & \quad \text{Exp: 2.356Å} \\
\text{K}^+ & \quad \text{Exp: 2.798Å}
\end{align*}
\]

Marcus, Y. Chem. Rev. 1988, 88, 1475
RDF Surfaces

Cl$^-$
Exp: 3.187Å

Br$^-$
Exp: 3.373Å
Future Work

- Run lattice calculations for all nine crystals
- Finish TI convergence testing
  - Run simulations out to 60 ns to finalize box size, and production time
  - Determine non-bonded cutoff
  - Run a large number of lambda values to prove convergence
- Produce TI surfaces
- Test parameters
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