What can you do with a polarizable force field?

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Who am I?

Physics and Political Philosophy

High School Physics and Chemistry

Biophysics Ph.D.

Truman Fellowship
The Grand Challenge of Molecular Science

Can we predict the behavior of molecules at the atomic scale?

\[ F = ma \]

\[ H\Psi = E\Psi \]
The Standard: Point Charge Force Field

\[ U = \sum \frac{1}{2} K_b (b - b_0)^2 + \sum \frac{1}{2} K_\theta (\theta - \theta_0)^2 + \sum K_\phi [1 - \cos(n\phi + \delta)] + \sum \epsilon \left[ (r_{ij})^2 - 2(r_{ij})^6 \right] + \sum \frac{332 q_i q_j}{r} \]

Fig. 1 The peptide backbone (a carbons) and disulphide bonds of PTL, a: X-ray structure\(^a\), b: Time evolved structure after 3.2 ps of dynamical simulation.
Atoms respond to their environment

Example: Ion Channel

AMOEBA has induced dipoles

\[ E_{AMOEBA} = E_{pair} + E_{pol} \]
AMOEBA Simulations of KcsA

Is there water in the channel or not?

4 ions is most stable

The free energy profile is consistent

AMOEBA predicts no water in the channel

Jing, Rackers, et al. Chemical Science, 2021
AMOEBA still has errors because it is point-based.
HIPPO: Hydrogen-Like Intermolecular Polarizable Potential

Point Force Fields

HIPPO

$U_{\text{intermolecular}} =$

Electrostatics + Polarization +
Dispersion + Pauli Repulsion

$ab\ \text{initio}$ SAPT
HIPPO: Hydrogen-Like Intermolecular Polarizable Potential

HIPPO gets base stacking right.
HIPPO: Hydrogen-Like Intermolecular Polarizable Potential

HIPPO gets drug binding interactions right.
The HIPPO water model – Radial Distribution function

Rackers, Silva, Wang and Ponder, ArXiv 2021
The HIPPO water model – Temperature Dependence

Density vs. Temperature

Dielectric Constant vs. Temperature

Surface Tension vs. Temperature
 HIPPO for small molecules - preliminary

<table>
<thead>
<tr>
<th>Compound</th>
<th>HIPPO Density</th>
<th>Experimental Density</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetamide</td>
<td>1</td>
<td>1.09</td>
</tr>
<tr>
<td>Acetic Acid</td>
<td>1</td>
<td>1.09</td>
</tr>
<tr>
<td>Methanol</td>
<td>0.5</td>
<td>0.79</td>
</tr>
<tr>
<td>Methylacetamide</td>
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<tr>
<td>Methylamime</td>
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<td>0.79</td>
</tr>
<tr>
<td>MethylBromide</td>
<td>1.5</td>
<td>1.85</td>
</tr>
<tr>
<td>MethylChloride</td>
<td>1</td>
<td>1.09</td>
</tr>
<tr>
<td>MethyleneBromide</td>
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<td>MethyleneChloride</td>
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<td>1.85</td>
</tr>
<tr>
<td>Pyrrolidine</td>
<td>0.5</td>
<td>0.79</td>
</tr>
</tbody>
</table>
Why is HIPPO more accurate?

HIPPO is a closer approximation of intermolecular physics than any preceding Biomolecular Force Field.

Electrostatic Potential Error at the vdW surface

HIPPO

Multipole Only
Outlook

AMOEBA
- Polarization can give accurate protein simulations.
- We have done the first AMOEBA ion channel predictions.

HIPPO
- Corrects the error(s) due to point approximation.
- Closely follows quantum mechanics.
- Produces very accurate model for water. Protein model soon.

Code
- AMOEBA/HIPPO presently available for GPUs on Tinker9 and OpenMM.
- AMOEBA/HIPPO coming to a LAMMPS release very soon!
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