

10/14/2024

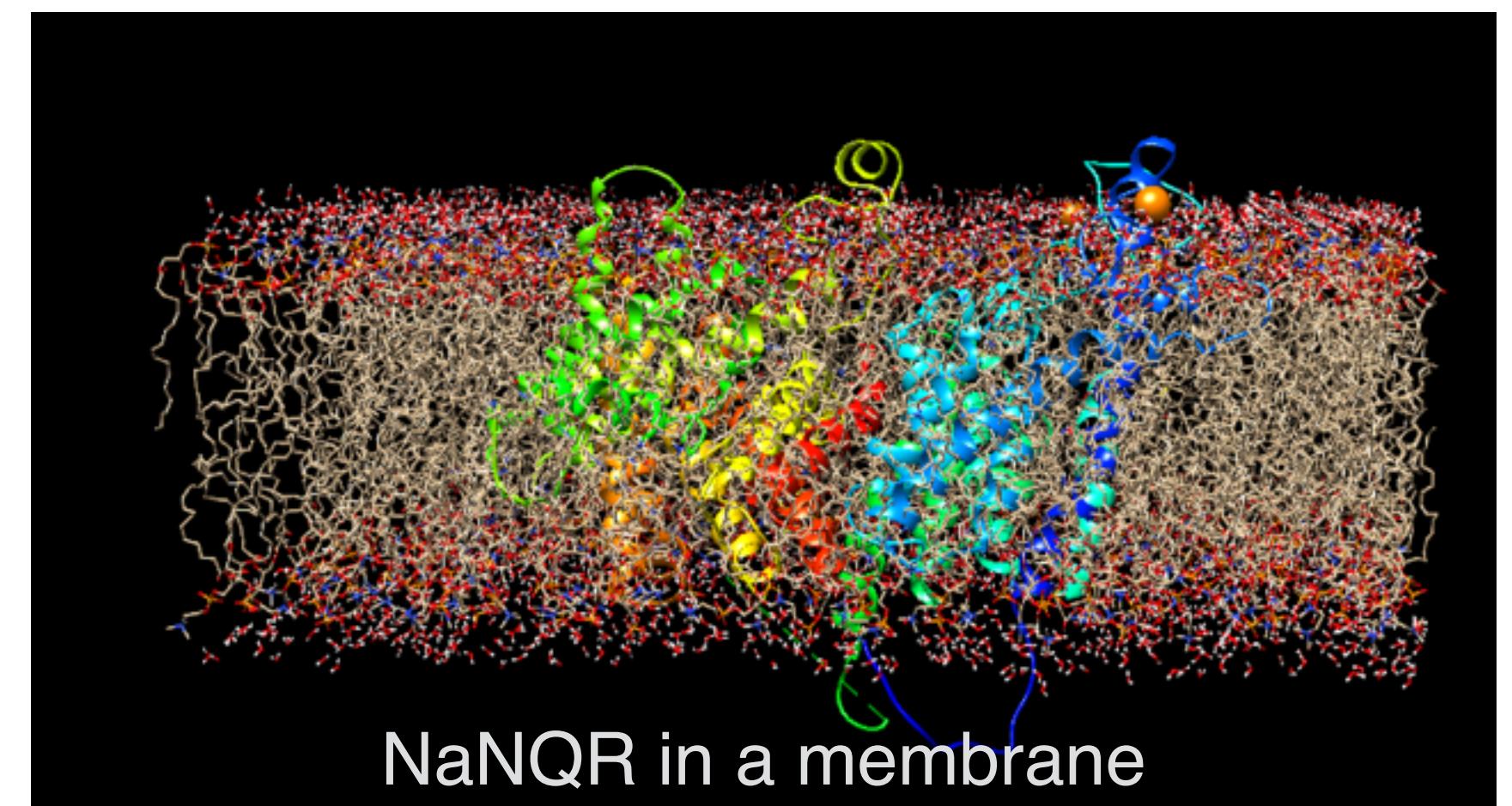
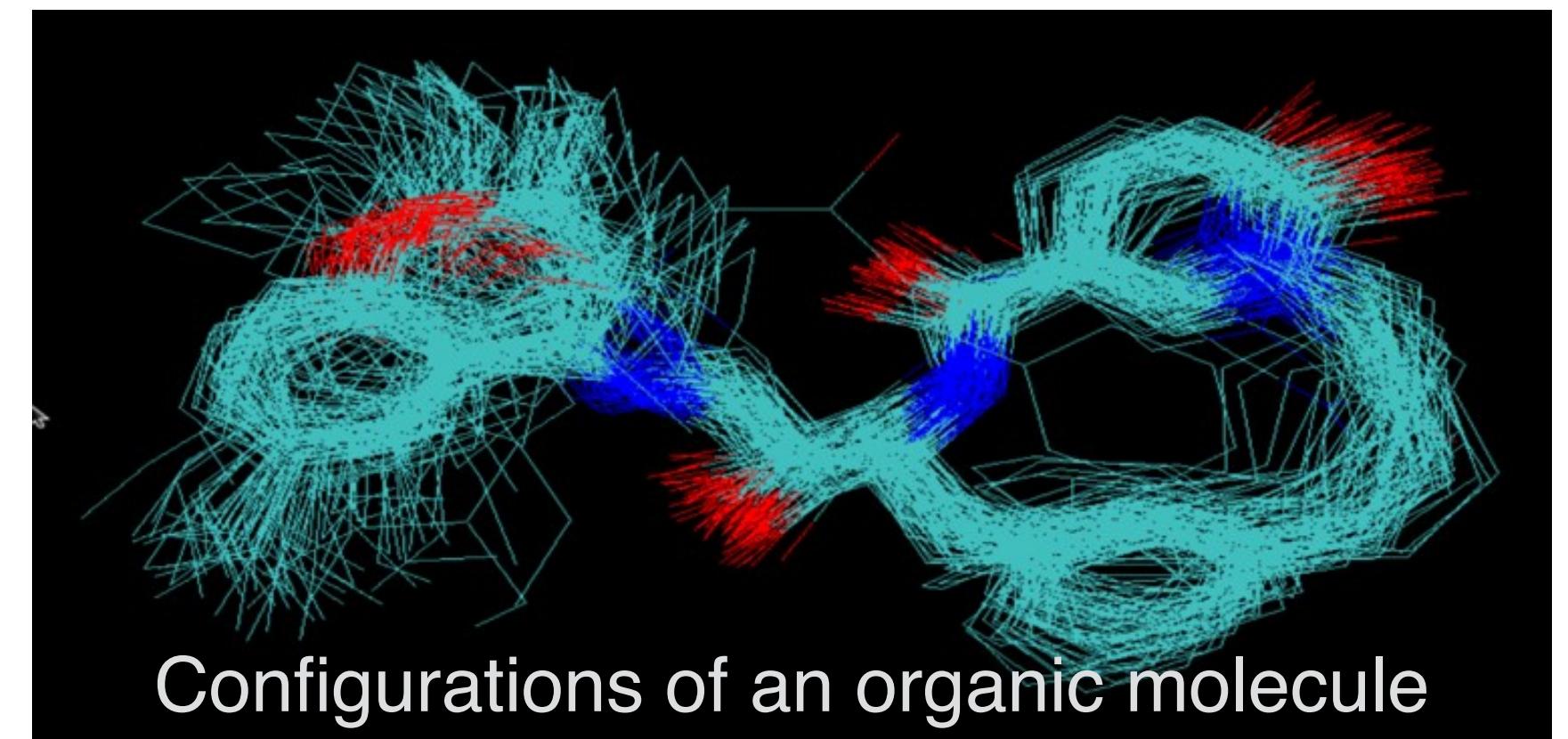
- Today's lecture is intended to help you achieve the following learning objective:
Summarize the purpose of a molecular mechanics force field. Identify the terms in the molecular mechanics force field.
- Molecular mechanics force fields
 - What are they?
 - How are they useful?
 - What are made of?
 - What are their limitations?
- Final project
 - Overview
 - Team meeting

Molecular Mechanics Force Fields

What are molecular mechanics force fields?

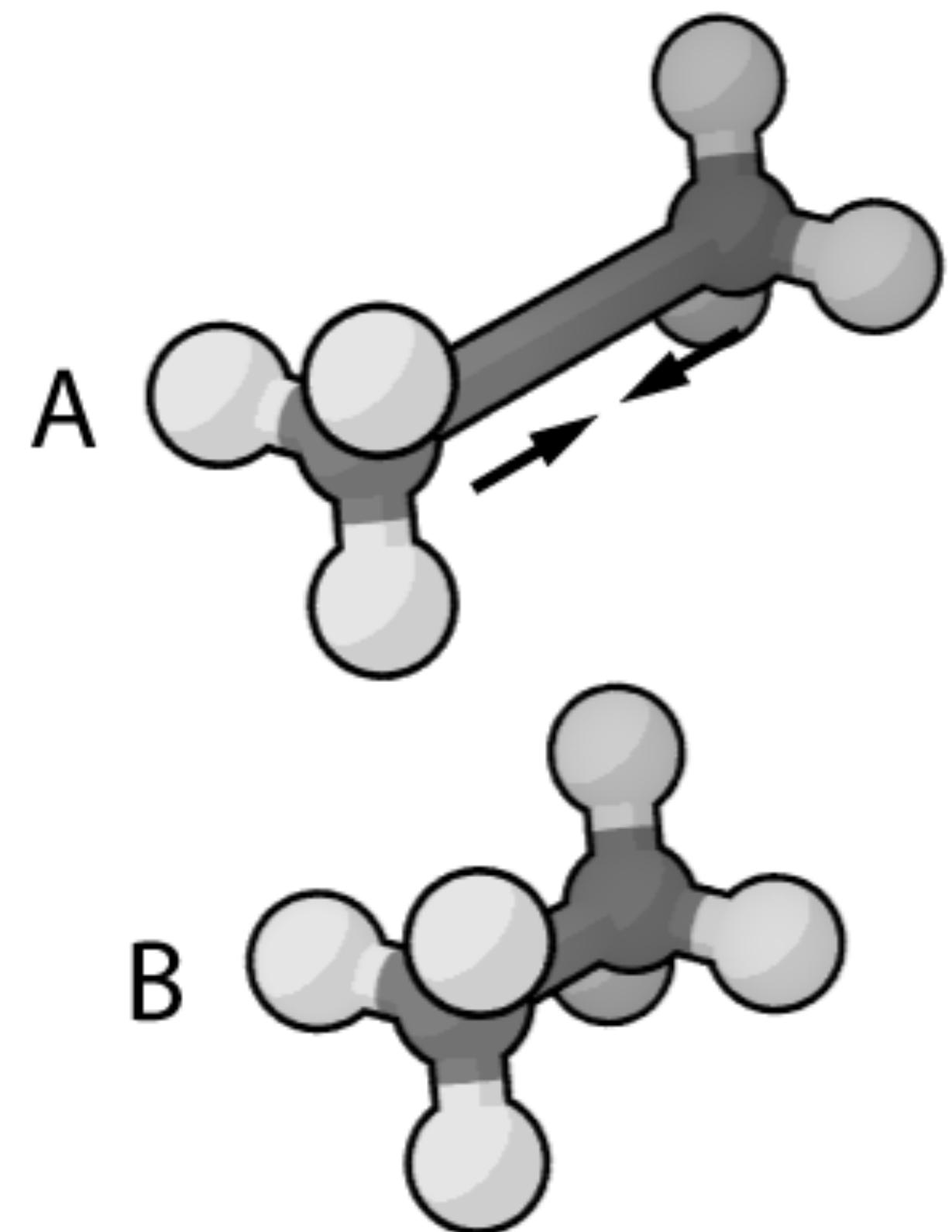
- **E(x)** - an equation describing the energy of a configuration of particles
- Input: positions of particles in a system
 - particles are usually atoms, but can be
 - collections of atoms (e.g. amino acid) in coarse-grained force fields
 - electrons pairs in a Drude oscillator model
- Output: potential energy

Some systems described by molecular mechanics

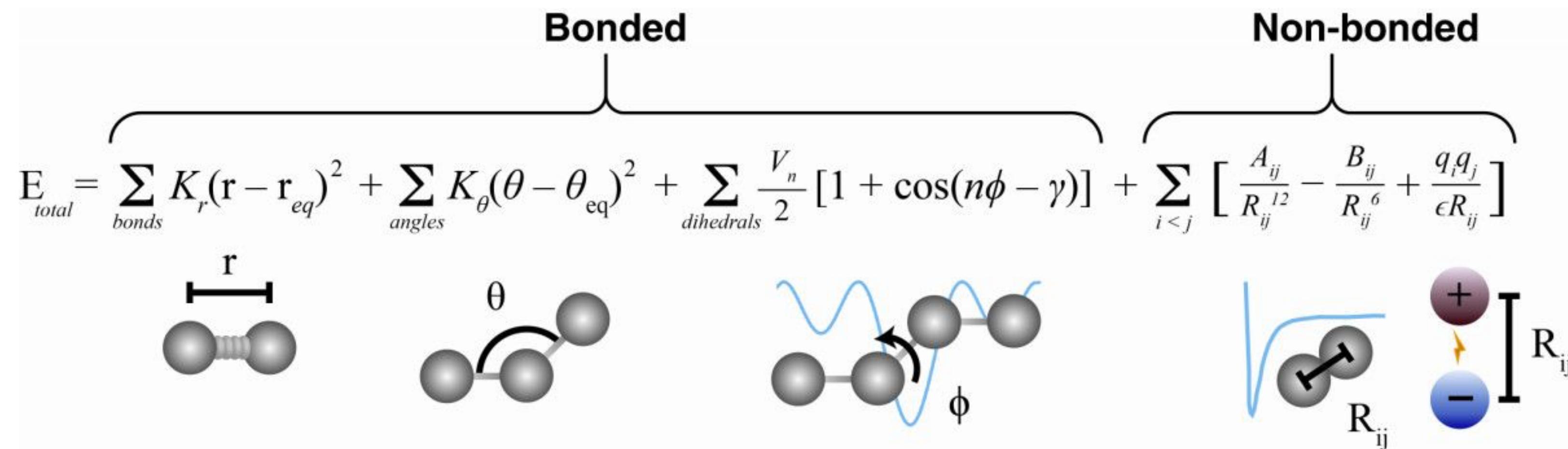


How are they useful?

- Energy optimization provides reasonable structures
 - Helpful for building models that fit to experiment.
 - AMBER (Assisted Model Building with Energy Refinement) is a popular force field.
- Basis for many scoring functions in molecular docking.
- Gradients are helpful for optimization and to calculate forces in molecular dynamics simulations
- According to the Boltzmann distribution, energies specify probabilities, $p(x) \propto e^{-\beta E(x)}$.



What are they made of?



From Figure 3 of
Durant and McCammon, 2011

The potential energy of a system can be divided into those caused by interactions between atoms that are chemically bonded to one another and those caused by interactions between atoms that are not bonded. Chemical bonds and atomic angles are modeled using simple springs, and dihedral angles (that is, rotations about a bond) are modeled using a sinusoidal function that approximates the energy differences between eclipsed and staggered conformations. Non-bonded forces arise due to van der Waals interactions, modeled using the Lennard-Jones potential, and charged (electrostatic) interactions, modeled using Coulomb's law.

Taken from Figure 3 of Durrant & McCammon, 2011.

Bonded Interactions

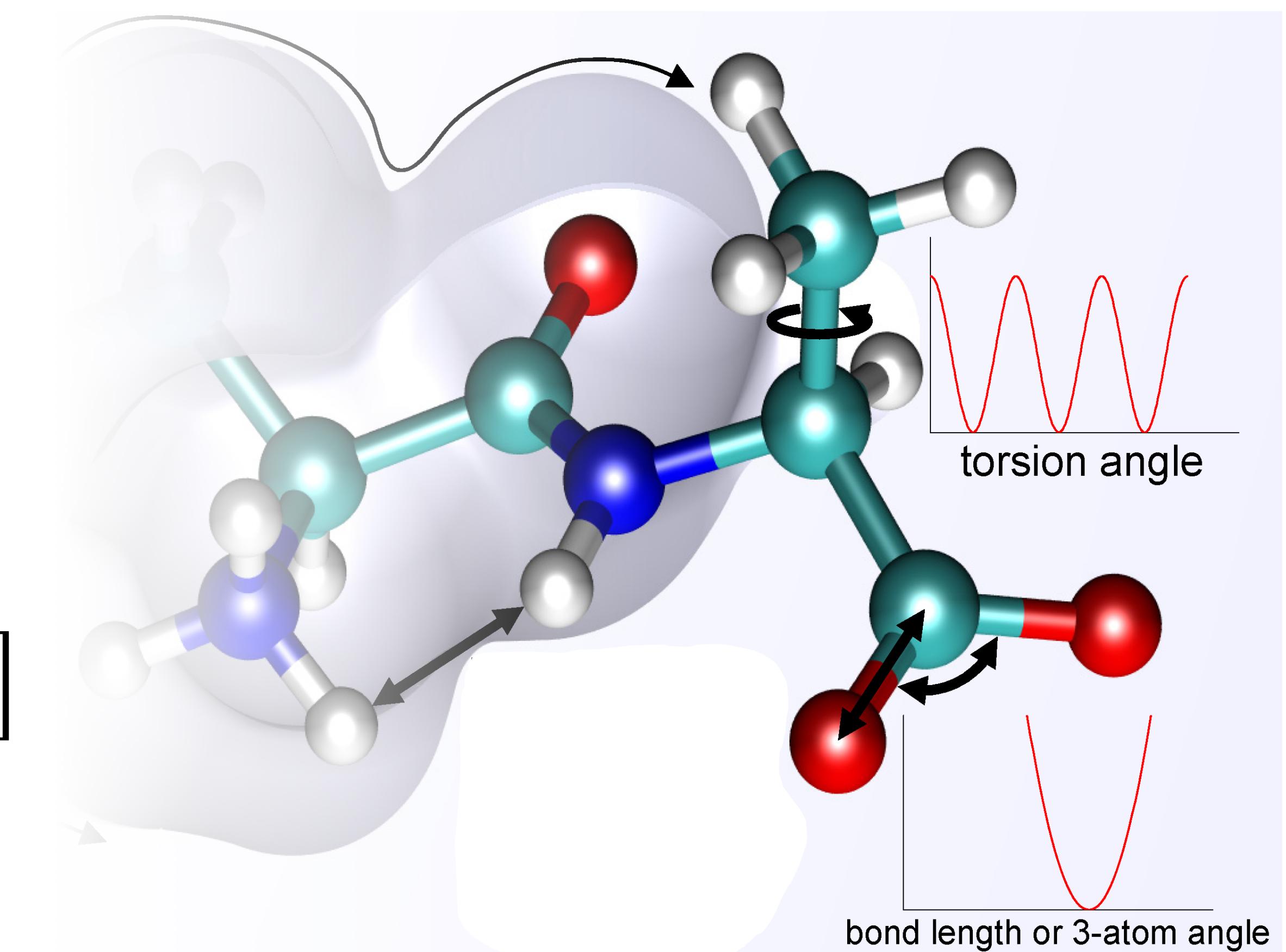
are between atoms that are covalently linked by three or fewer bonds

$$E_{bonds} = \sum_i^{Bonds} \frac{k_i}{2} (x_i - x_{i,o})^2$$

$$E_{angles} = \sum_i^{Angles} \frac{k_i}{2} (\omega_i - \omega_{i,o})^2$$

$$E_{torsions} = \sum_i^{Torsions} \frac{V_i}{2} [1 + \cos(n_i\phi_i - \gamma_i)]$$

$$E_{bonded} = E_{bonds} + E_{angles} + E_{torsions}$$



Nonbonded Interactions

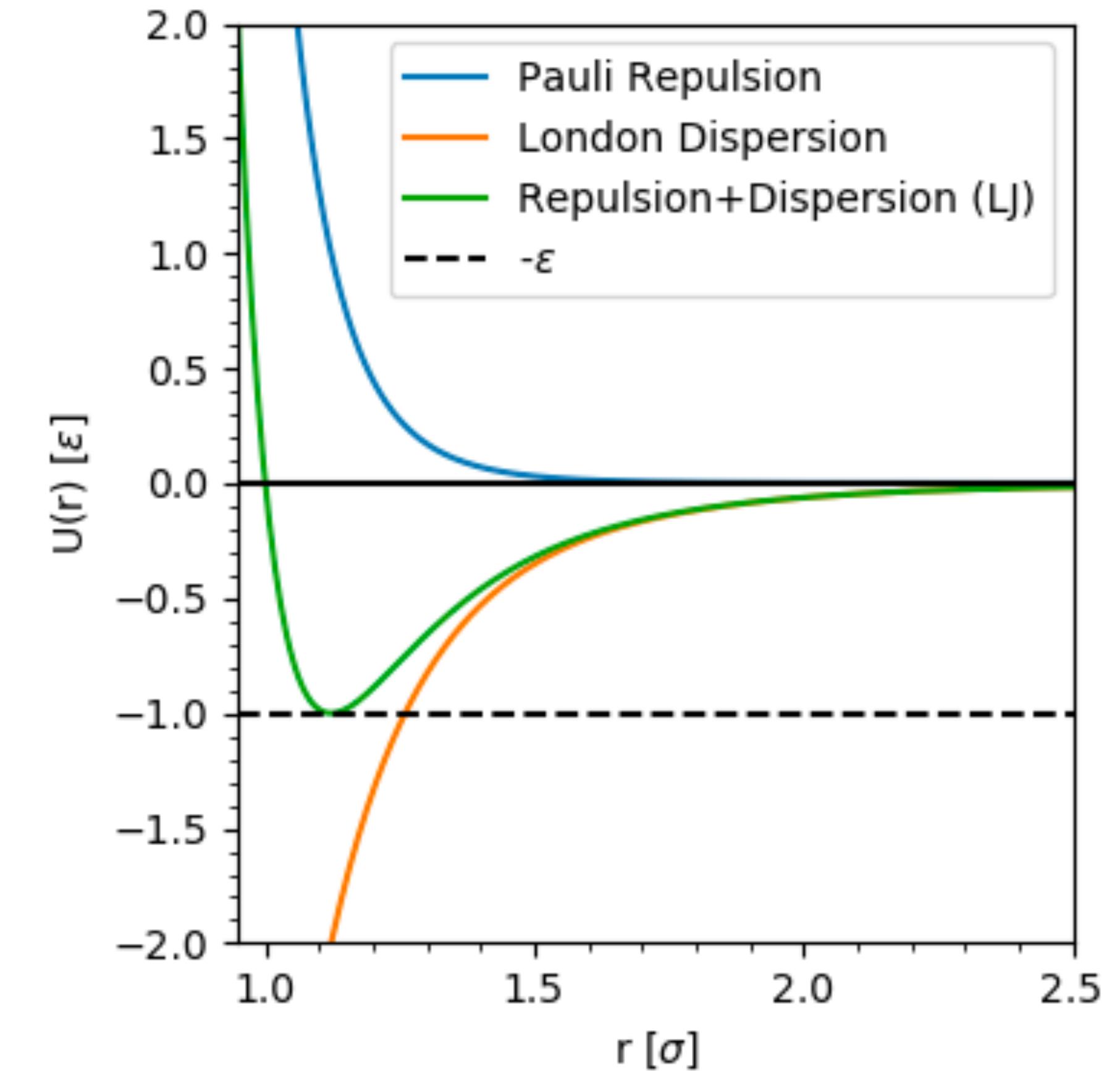
are between atoms that are not covalently linked or linked by more than three bonds

$$E_{Coloumbic} = \sum_{i,j}^{Atoms \ with \ i < j} \frac{q_i q_j}{\epsilon R_{i,j}}$$

$$E_{Lennard-Jones} = \sum_{i,j}^{Atoms \ with \ i < j} \frac{A_{i,j}}{R_{i,j}^{12}} - \frac{B_{i,j}}{R_{i,j}^6}$$

based on $4\epsilon \left[\left(\frac{\sigma}{r}\right)^{12} - \left(\frac{\sigma}{r}\right)^6 \right]$

$$E_{Non-Bonded} = E_{Coloumbic} + E_{Lennard-Jones}$$



Where do parameters come from?

- QM + experiment
- AMBER (as discussed in Tian 2020)
 - “we also included in ff14SB a small empirical adjustment to ff99SB (using TIP3P water) to improve agreement with NMR data for short alanine peptides”
 - Quantum chemistry data in implicit solvent (opposed to gas)
- OpenFF 2.0.0 (<https://openforcefield.org/force-fields/force-fields/>)
 - A select set of the vdW parameters were trained against a set of experimental mass density and enthalpy of mixing measurements sourced from the NIST ThermoML archive.
 - A select set of the bond length, bond force constant, equilibrium angle, angle force constant and torsion barrier height parameters were trained against a set of QC computed optimized geometries and torsion profiles, whereby the output force field of the first step was used as the starting point.

SMIRNOFF specification, in Open Force Field

Specifying parameters

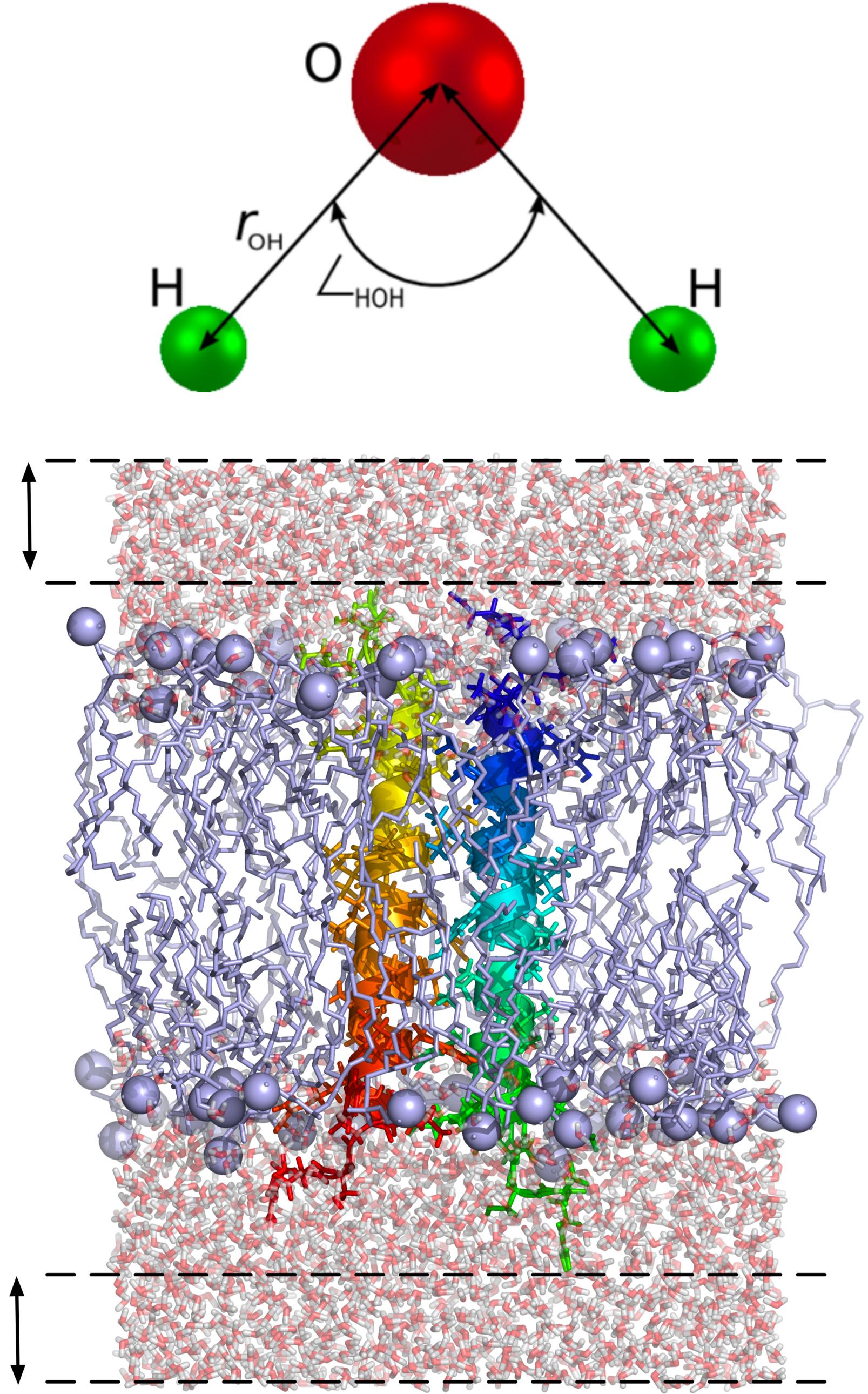
Under each of these force terms, there are tags for individual parameter lines such as these:

```
<Angles version="0.3" potential="harmonic">
  <Angle smirks="[a,A:1]-[#6X4:2]-[a,A:3]" angle="109.50*degree" k="100.0*kilocalorie*mole^-1*angstrom^2">
    <Angle smirks="#1:[1]-[#6X4:2]-#1:3" angle="109.50*degree" k="70.0*kilocalorie*mole^-1*angstrom^2">
  </Angles>
```

The first of these specifies the `smirks` attribute as `[a,A:1]-[#6X4:2]-[a,A:3]`, specifying a SMIRKS pattern that matches three connected atoms specifying an angle. This particular SMIRKS pattern matches a tetravalent carbon at the center with single bonds to two atoms of any type. This pattern is essentially a [SMARTS](#) string with numerical atom tags commonly used in [SMIRKS](#) to identify atoms in chemically unique environments--these can be thought of as tagged regular expressions for identifying chemical environments, and atoms within those environments. Here, `[a,A]` denotes any atom--either aromatic (`a`) or aliphatic (`A`), while `[#6X4]` denotes a carbon by element number (`#6`) that with four substituents (`X4`). The symbol `-` joining these groups denotes a single bond. The strings `:1`, `:2`, and `:3` label these atoms as indices 1, 2, and 3, with 2 being the central atom. Equilibrium angles are provided as the `angle` attribute, along with force constants as the `k` attribute (with corresponding units included in the expression).

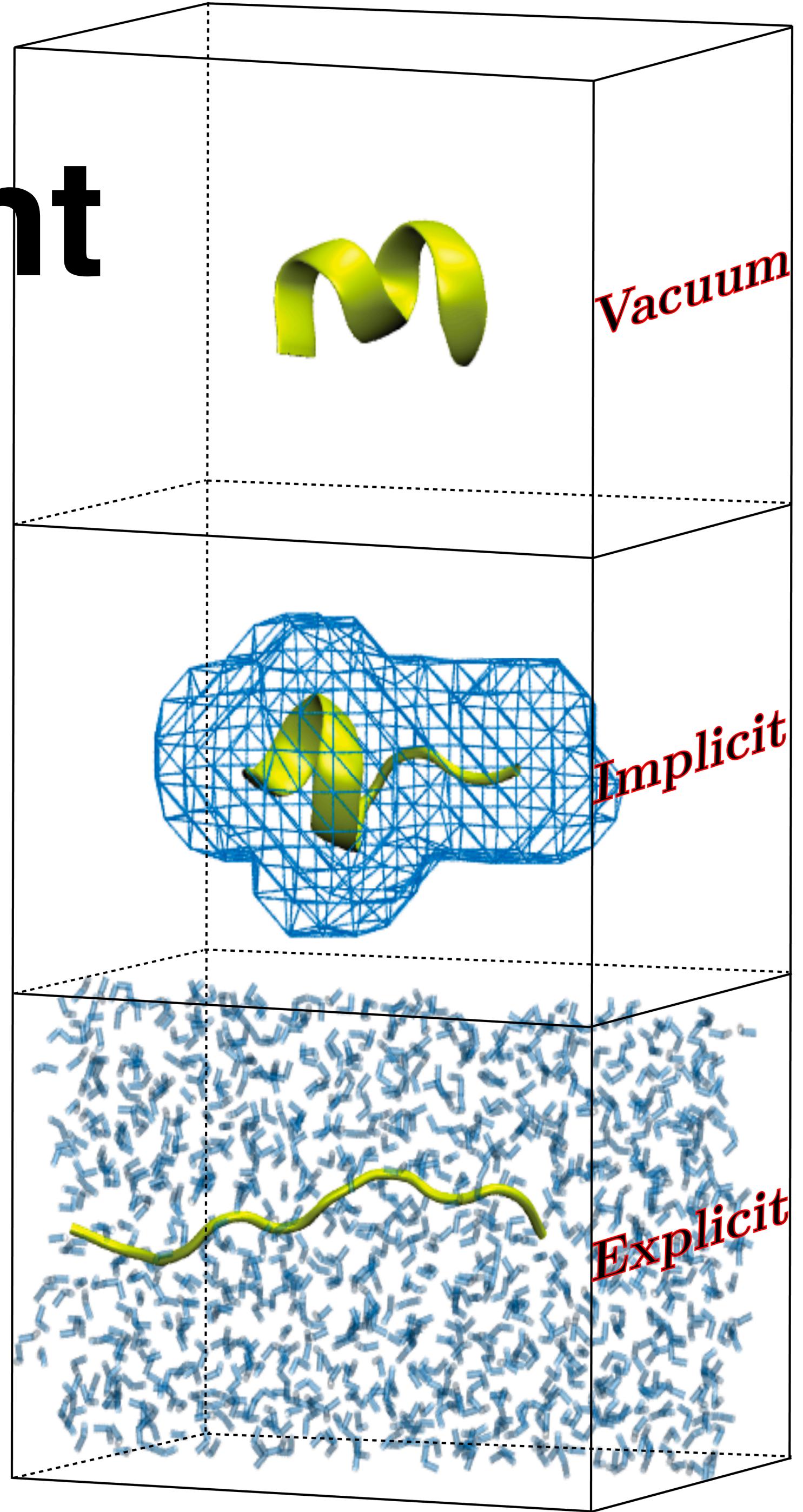
Solvent

- Usually water, but may be other solvents
- Ions
- Popular water models include
 - SPC (simple point charge)
 - TIP3P (transferable intermolecular potential with 3 points)
 - OPC (Optimal point charge), to reproduce electrostatics of water
- These have LJ site for O and two charge sites.



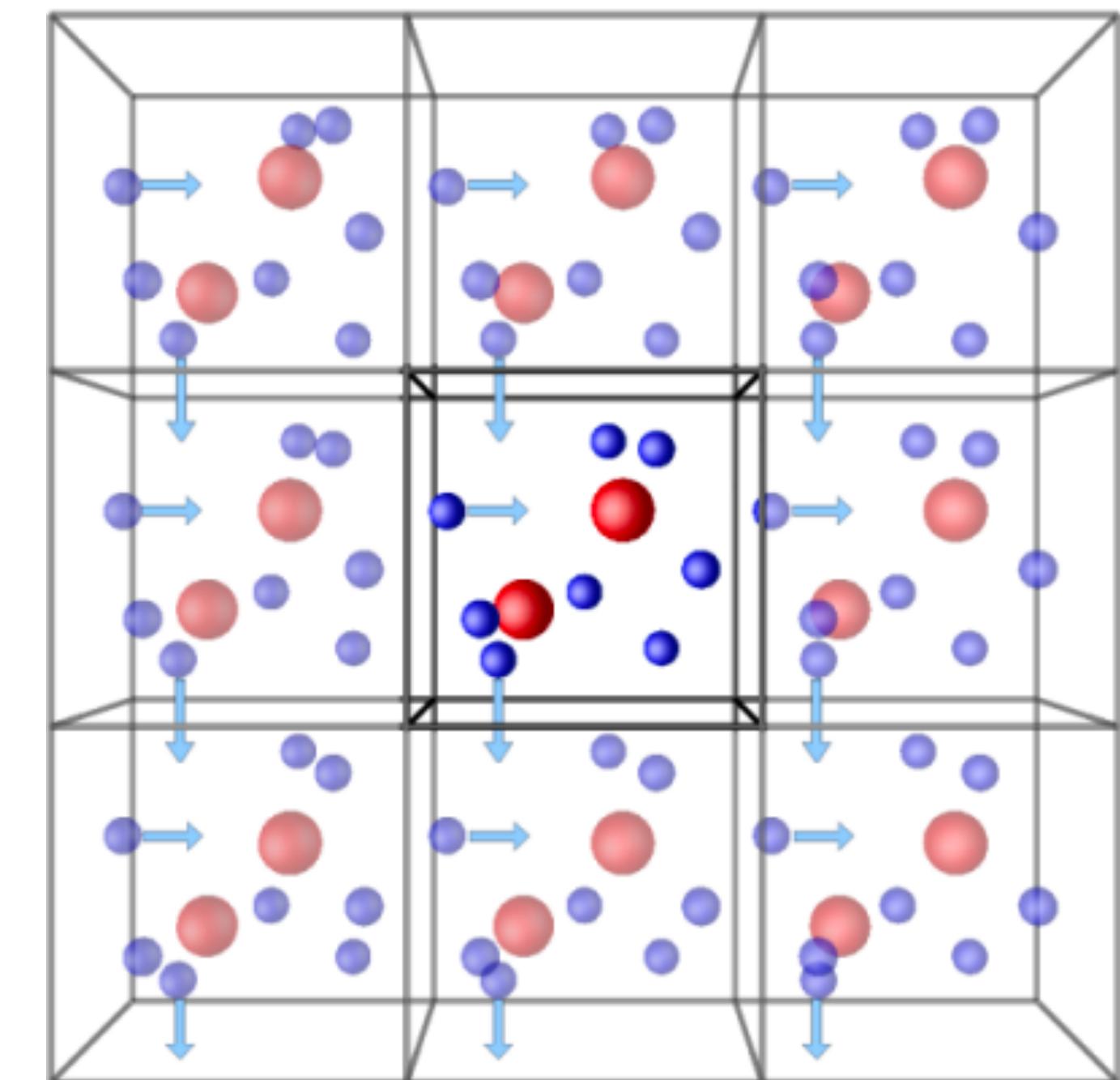
Implicit Solvent

- Solvent can make up a large fraction of atoms in a system and can dampen motions in a molecular simulation
- Explicit solvent - 3D positions are modeled in the system
- Implicit solvent - effects of solvent are modeled.
- Two popular models are Poisson-Boltzmann Surface Area (PB/SA) and Generalized Born Surface Area (GB/SA)
 - Poisson-Boltzmann equation used to describe electrostatic energy of inserting charges into solvent. Generalized Born approximates PB.
 - Nonpolar cavity formation energy based on surface tension x surface area of solute.



Periodic Boundary Conditions

- To mitigate boundary effects, unit cell assumed to be surrounded by infinite number of identical copies
 - Particles that pass through boundary reappear on the other side
 - Particles usually interact with closest image (minimum image convention)
- PBC affects energy
 - Short-range electrostatics treated by Coulomb's law
 - Long-range electrostatics treated by Ewald sum



<https://lammpstube.com/2019/10/30/periodic-boundary-conditions/>

What are their limitations?

- Potential energy less accurate than quantum mechanics. Based on Tian 2020, some key approximations are that
 - Bonded terms are independent and additive
 - Parameters are transferrable between molecules (e.g. from small organic molecules to proteins)
 - “The relative scarceness of experimental data compared to the number of parameters in the FF leaves the empirical fitting problem severely underconstrained.”
- Cannot model bond formation or breaking
- Popular fixed-charged force fields do not account for polarization

References

- Durrant, J. D.; McCammon, J. A. Molecular Dynamics Simulations and Drug Discovery. BMC Biol 2011, 9 (1), 71. <https://doi.org/10.1186/1741-7007-9-71>, adapted under the CC BY 2.0 license.
- Jo S, Kim T, Im W (2007) Automated Builder and Database of Protein/Membrane Complexes for Molecular Dynamics Simulations. PLoS ONE 2(9): e880. <https://doi.org/10.1371/journal.pone.0000880>, adapted under the CC BY 4.0 license.
- Bureau HR, Merz DR Jr, Hershkovits E, Quirk S, Hernandez R (2015) Constrained Unfolding of a Helical Peptide: Implicit versus Explicit Solvents. PLoS ONE 10(5): e0127034. <https://doi.org/10.1371/journal.pone.0127034>, adapted under the CC BY 4.0 license.
- Tian, C.; Kasavajhala, K.; Belfon, K. A. A.; Raguette, L.; Huang, H.; Migues, A. N.; Bickel, J.; Wang, Y.; Pincay, J.; Wu, Q.; Simmerling, C. Ff19SB: Amino-Acid-Specific Protein Backbone Parameters Trained against Quantum Mechanics Energy Surfaces in Solution. J. Chem. Theory Comput. 2020, 16 (1), 528–552. <https://doi.org/10.1021/acs.jctc.9b00591>.

Final Project

- Overview <https://daveminh.github.io/Chem456-2024F/assignments/>
- Team meeting
 - Q&A with target presenter
 - Brainstorm possible project goals
 - Discuss feasibility of ideas with me