Force Field Parameters

- This module will introduce you to:
  - What force fields are, and their application to molecular dynamics simulations.
  - Information contained in force field parameter files, and how it is utilized.
  - How force field parameter files are generated, and how force field parameters are chosen.

- At the conclusion of this module, you will:
  - Understand the physics behind force field calculations.
  - Parameterize your own biomolecular system.

Previously Learned

- Obtaining a structure
- Homology Modeling
- Electrostatic Calculations of a Structure
- Docking a Ligand

Workshop Outcomes

- Running and Analyzing
  - Molecular Dynamics Simulations
  - Binding Free Energy Calculations

What is a force field?

Although force field parameters are stored in large files, they are not the force field.

The Force Field is: The equation describing the energy of a configuration of atoms.

Force Field Parameters are: The constants that are applied to chemically unique atoms.

How is this energy calculated?

Summation of:	Bonded Interactions
	Non-bonded Interactions
(and sometimes)	Implicit Solvent Interactions

Bonded Interactions

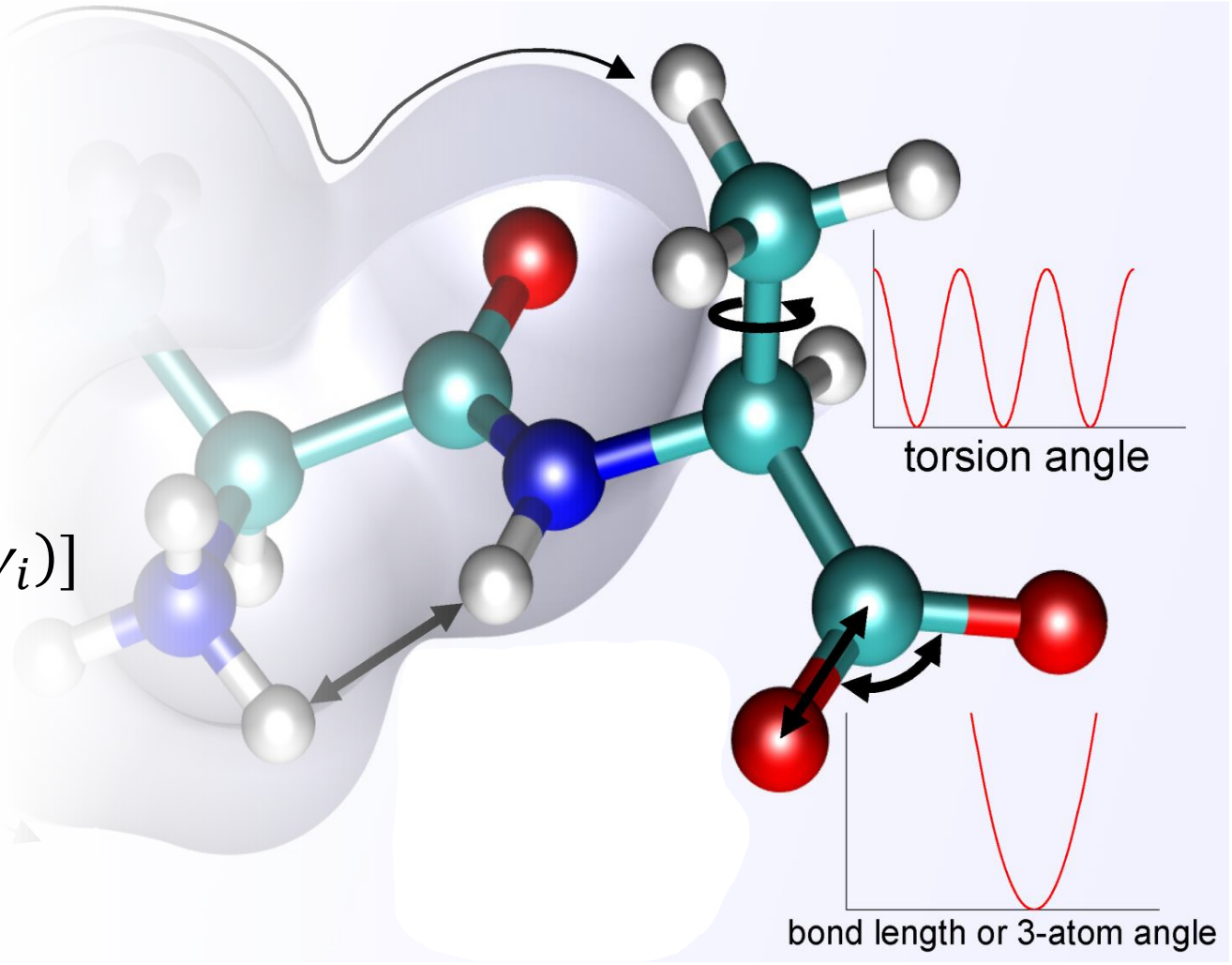
Interactions between atoms which are covalently linked by three or fewer bonds.

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

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

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

$$E_{Bonded} = E_{Bonds} + E_{Angles} + E_{Torsions}$$



Nonbonded Interactions

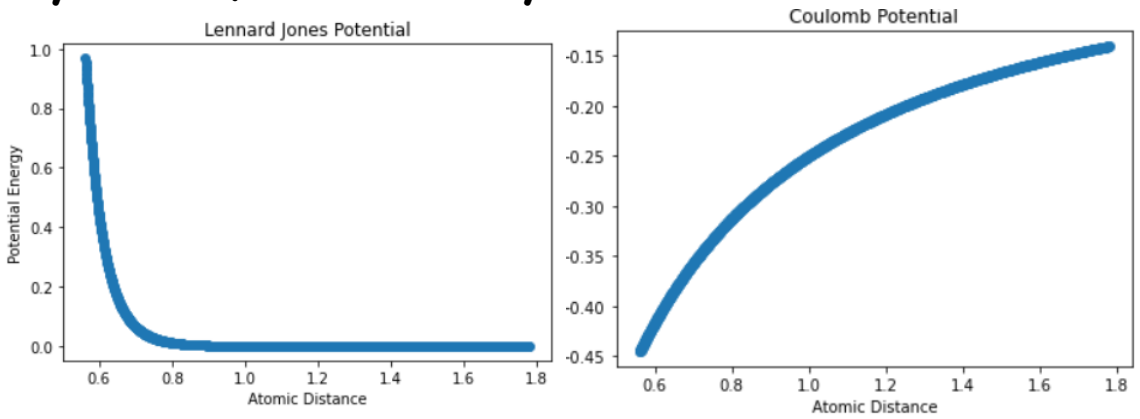
Interactions between atoms which are not covalently linked, or linked by more than 3 bonds.

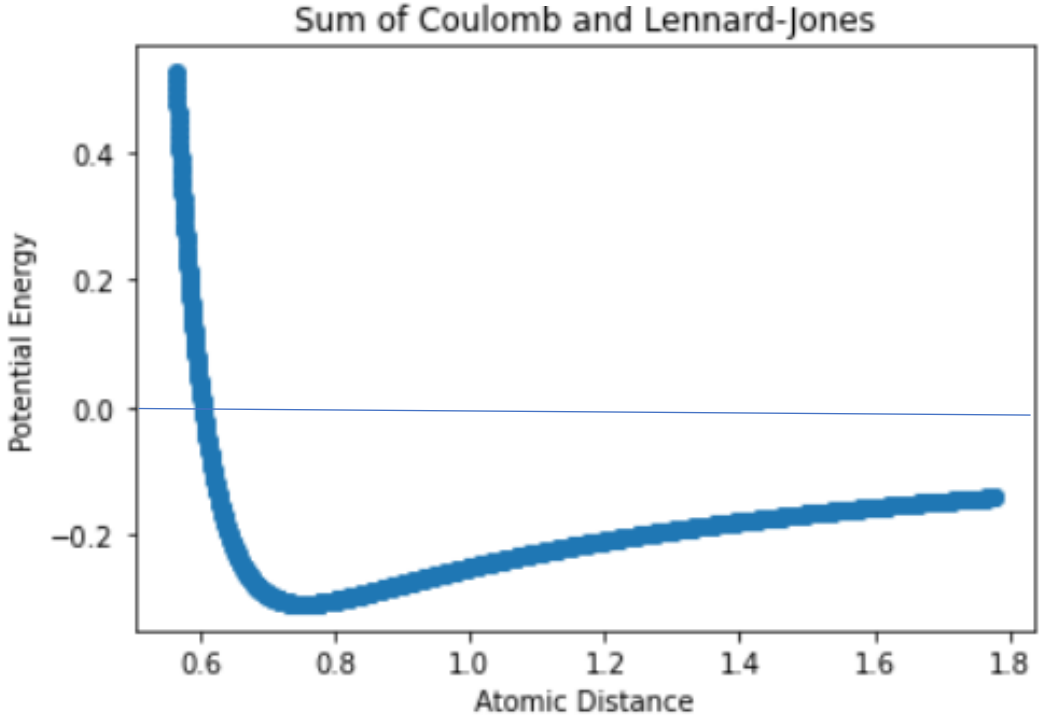
$$E_{Coloumbic} = \sum_{i,j}^{Atoms\ with\ i<j} \frac{q_i q_j}{\epsilon R_{i,j}}$$

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

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

At right, is an example of these potentials for two particles with opposite charge.





Implicit and Explicit Solvent Interactions

Interactions between implicit/explicit solvent and the modelled molecules.

Implicit Solvent

Water molecules are not present in the simulation, but are accounted for by calculation.

Compare and Contrast

Computational Expense

Accuracy

Explicit Solvent

Water (or other solvent) molecules are <u>actually present</u> in the simulation.

$$E_{Total} = E_{Bonded} + E_{Non-Bonded} + (E_{Solvent})$$

How Are Force Field Parameters Chosen?

Force Fields must parameterize:

Proteins Nucleic Acids Small Molecules Membranes

Historically, for fields were parameterized with values determined from gas-phase QM calculations.

Quantum is highly accurate for systems that are feasible to calculate.

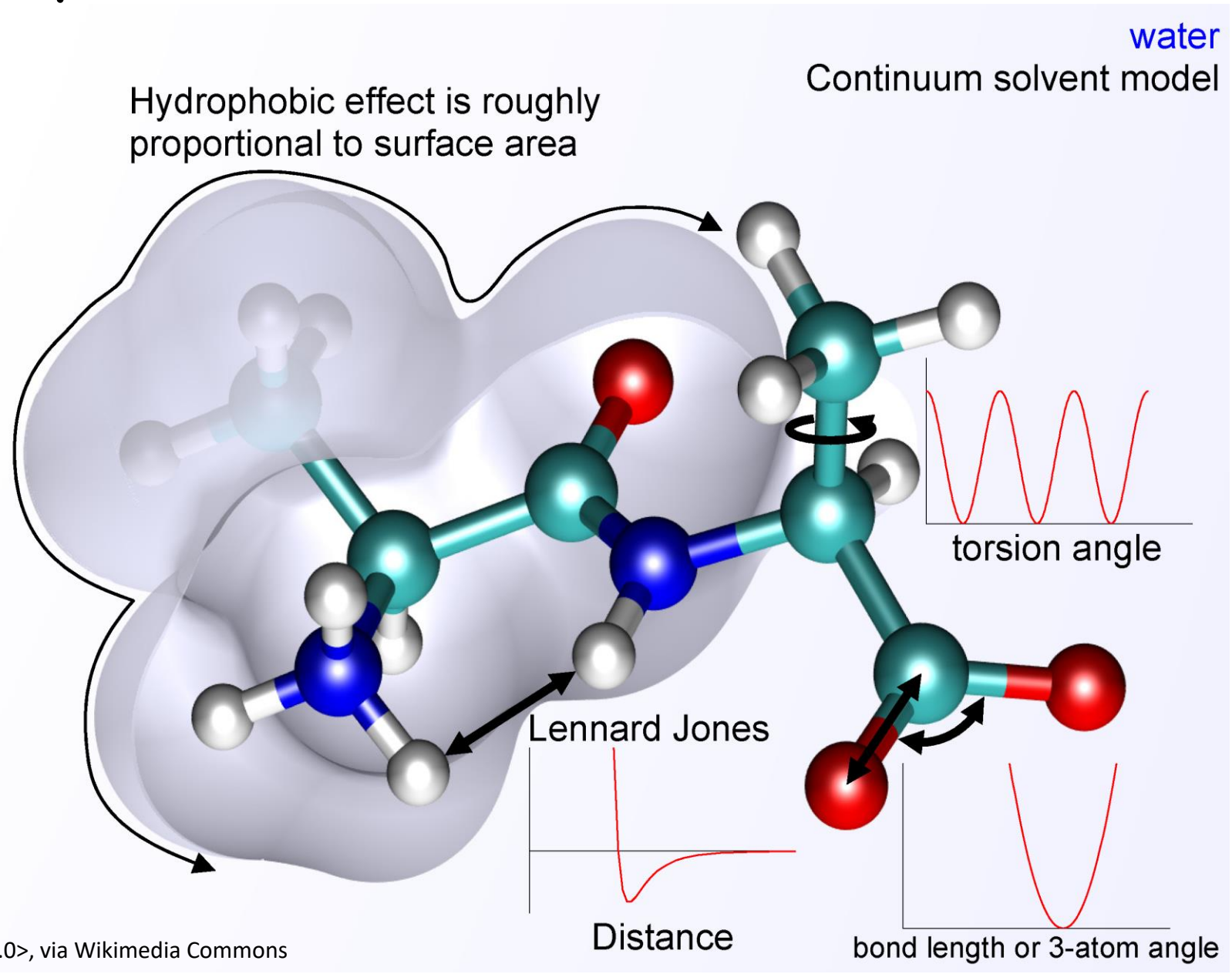
Correlation between gas and condensed phases is still not strong enough.

Today (literally), open-source protocols (Openmm and Ambertools) are available.

Amber force field can be applied to new molecules.

What do force fields specify that structure files do not? – Discuss!

- Atoms
  - Hybridization, (Mass)
  - Charge
- Bonds
  - Bond Order
  - Length and Spring Constant
- Angles
  - Optimal 3-atom Angle
  - Force Constant
- Torsions
  - Periodicity
  - Torsional Force Constant
- More!
  - Lennard Jones Parameters
  - Hydrophobic Surface Area



Short Quiz

What information is specified in force field files, but not structure files?

How are **bonded** interactions defined here, and accounted for?

How are **nonbonded** interactions defined here, and accounted for?

Lab-Overview

Necessary Input : .pdb file describing the docked drug's coordinates.

TASK 1 : Add hydrogens to the protein, parameterize it, and observe it's net charge.

TASK 2 : Add hydrogens to the ligand (docked drug), parameterize it, and save the parameters.

TASK 3 : Create a pdb file of the complex (the protein and ligand together in one file)

Add explicit water and ions (and membrane if applicable) to create a system.

Parameterize the entire system.

After completion of these tasks, you will have all necessary input files in order to perform molecular dynamics simulations on the paxlovid-Mpro system.

Lab – File Names and Meanings

File Ending:	Name/Meaning:
.pdb	Protein Data Bank structure file
.pqr	A pdb, which includes charge (q) and radius (r)
.pdbqt	A pdb, which includes Gasteiger charges (q) and Autodock atom type (t), this file type is specific to Autodock
.mol2	SYBYL format structure File, describes structure in SYBYL format as opposed to .pdb
.frcmod	A parameter file that can be loaded into tleap and have missing parameters filled by antechamber
.xml	A general parameter file complementary to .pdb
.prmtop	AMBER parameter topology file – completely describes the parameters of your system
.inpcrd	AMBER structure file – describes the coordinates of the atoms