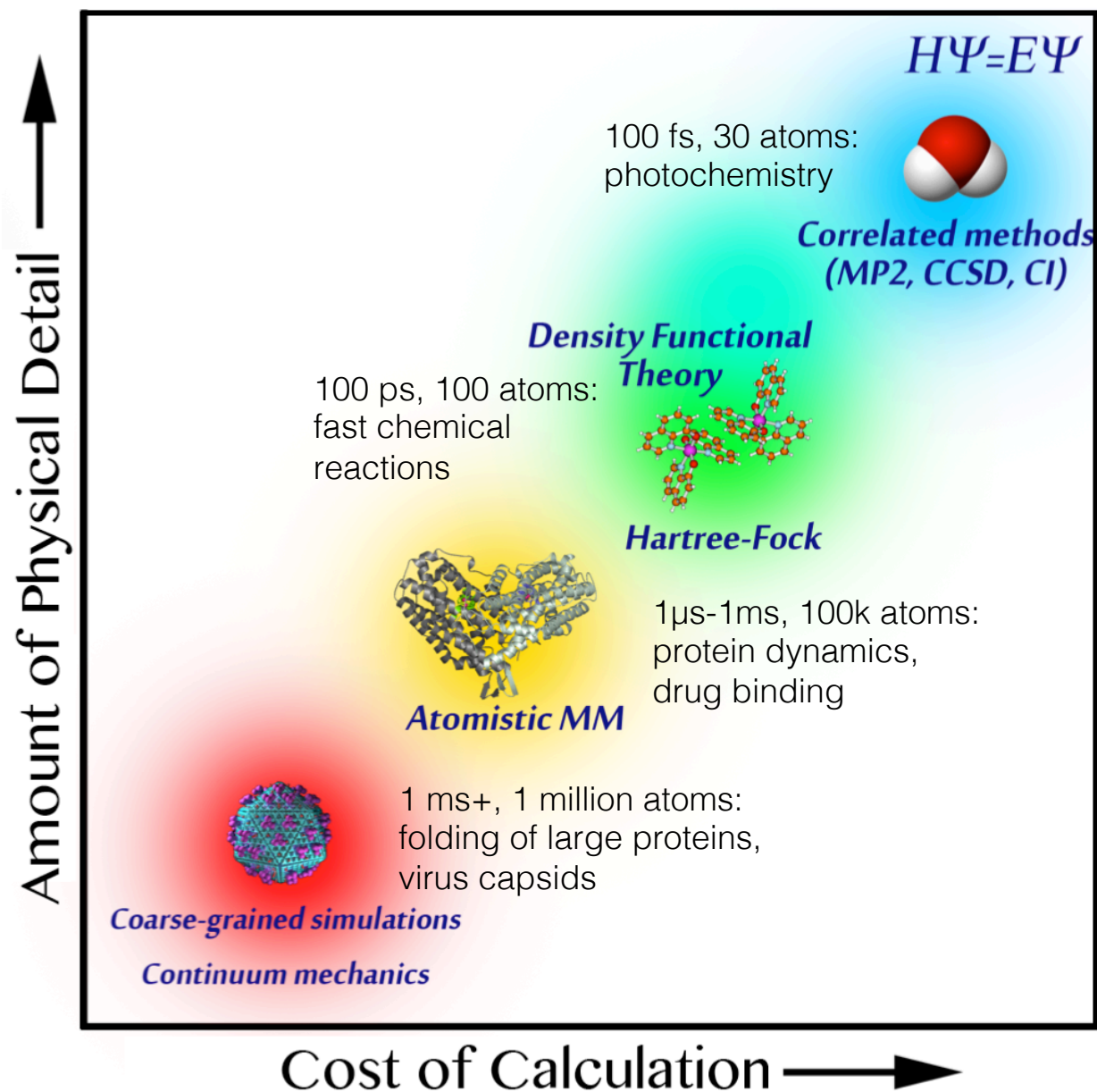


# **Introduction to molecular mechanics**

Lee-Ping Wang

Paul Nerenberg

# A bird's eye view of computational chemistry



- Computer simulations of molecules span a wide range of resolutions
- More detailed theories can describe complex phenomena and offer higher accuracy
- Less detailed theories allow for simulation of larger systems/longer timescales
- Empirical force fields are the method of choice in the simulation of biomolecules

# The Schrödinger equation

All ground-state quantum chemistry is based on the time-independent Schrödinger equation:

$$\hat{H}\Psi = E\Psi$$

$$(\hat{T} + \hat{V})\Psi = E\Psi$$

$$\left( -\sum_i \frac{\nabla_i^2}{2} + \sum_{I \neq J} \frac{Z_I Z_J}{|\mathbf{R}_I - \mathbf{R}_J|} - \sum_{i,I} \frac{Z_I}{|\mathbf{R}_I - \hat{\mathbf{r}}_i|} + \sum_{i \neq j} \frac{1}{|\hat{\mathbf{r}}_i - \hat{\mathbf{r}}_j|} \right) \Psi(\mathbf{r}_i; \mathbf{R}_I) = E(\mathbf{R}_I) \Psi(\mathbf{r}_i; \mathbf{R}_I)$$

Kinetic  
energy  
operator

Nuclear  
repulsion  
...just a number

Electron-  
nuclear  
attraction

Electron-  
electron  
repulsion

Electron  
wavefunction

Electronic  
energy

## Born-Oppenheimer approximation:

when solving for the electronic wavefunction, treat nuclei as static external potentials

# Useful results from quantum chemistry

## Electronic structure

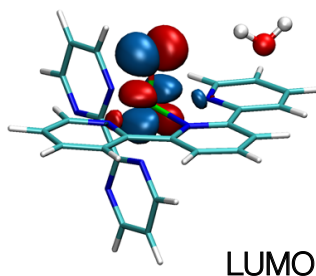
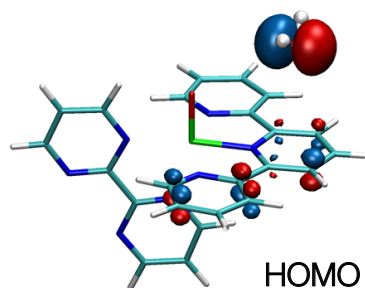
Molecular orbitals can provide a detailed explanation of reaction mechanisms

## Spectra

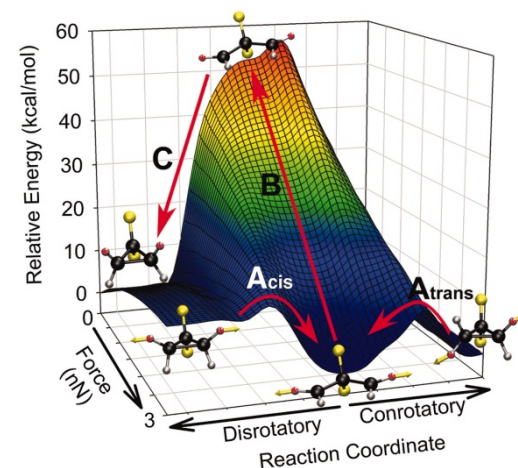
Computing spectra helps us compare with experiment and study molecular interactions with light (may require *time-dependent* calculations for electrons)

## Potential energy surface

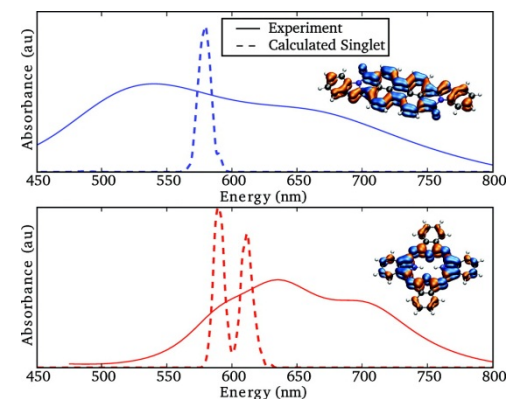
Evaluating the potential energy and its gradients allows us to simulate how molecules move



Wang, Wu, and Van Voorhis,  
*Inorg Chem* (2011).



JM Lenhardt, et al.  
*Science* (2010).



Yost, Wang, and Van Voorhis  
*J Phys Chem B* (2011).

# Approximate solutions to the SE

Schrödinger's equation is nearly impossible to solve, so approximate methods are used.

$$\left( -\sum_i \frac{\nabla_i^2}{2} - \sum_{i,I} \frac{Z_I}{|\mathbf{R}_I - \hat{\mathbf{r}}_i|} + \sum_{i \neq j} \frac{1}{|\hat{\mathbf{r}}_i - \hat{\mathbf{r}}_j|} \right) \Psi(\mathbf{r}_i) = E \Psi(\mathbf{r}_i)$$

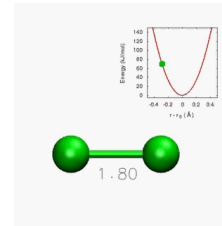
$$|\Psi\rangle_{\text{HF}} = \begin{vmatrix} \chi_1(1) & \chi_1(2) & \cdots & \chi_1(N) \\ \chi_2(1) & \chi_2(2) & \cdots & \chi_2(N) \\ \vdots & \vdots & \ddots & \vdots \\ \chi_N(1) & \chi_N(2) & \cdots & \chi_N(N) \end{vmatrix}$$

**Slater determinant:** wavefunction of *noninteracting* electrons for interacting system

$$\rho_0(\mathbf{r}) \leftrightarrow \Psi_0(\mathbf{r}_1, \mathbf{r}_2, \mathbf{r}_3, \dots, \mathbf{r}_N) \rightarrow E$$

**Density functional theory:** ground-state electron density contains all information in the ground-state wavefunction

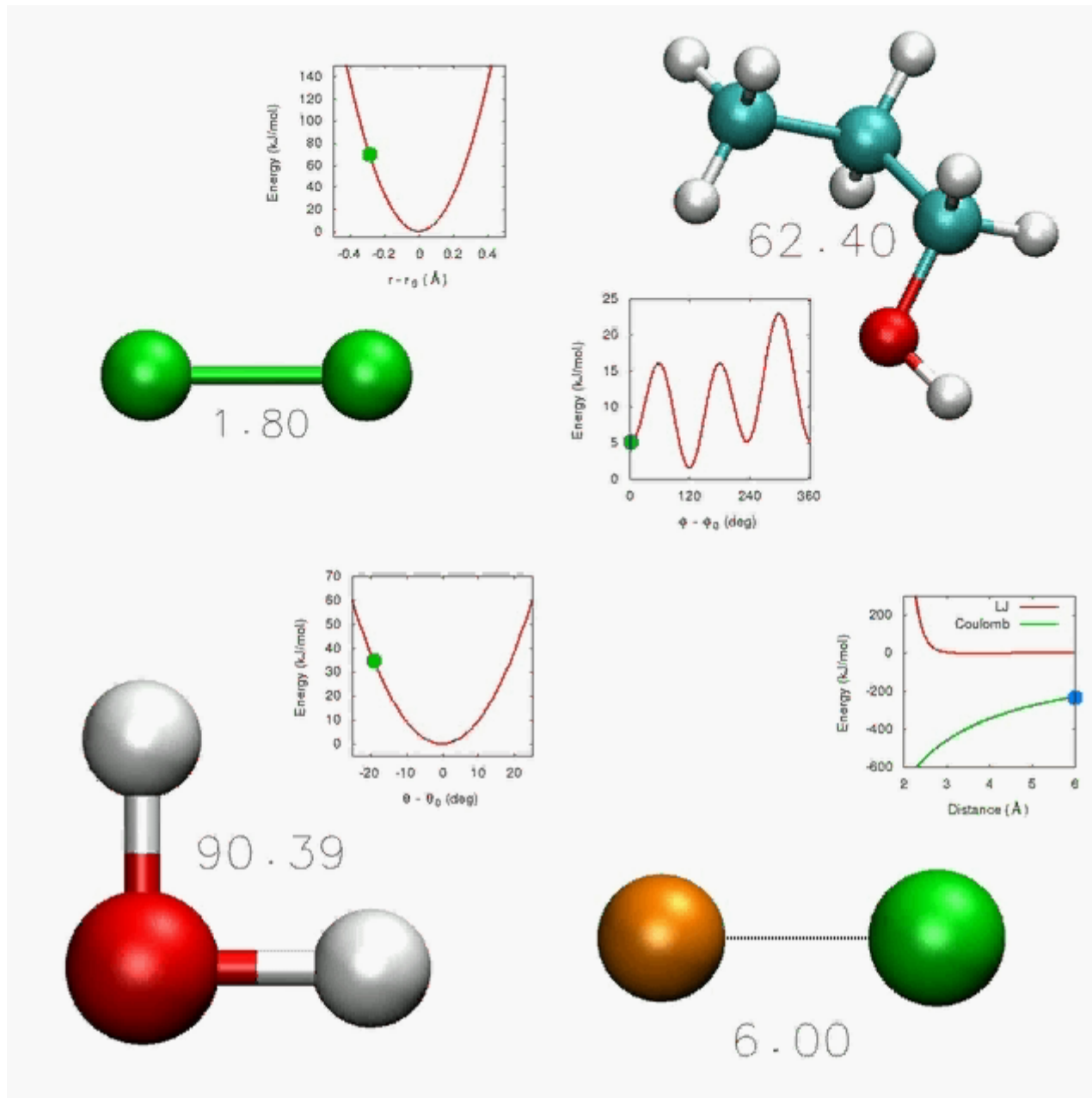
- Electron repulsion makes this problem difficult
- **Approach 1:** Use approximate wavefunction forms (quantum chem.)
- **Approach 2:** Use the electron density as the main variable
- **Approach 3:** Approximate the energy using empirical functions



$$E(\mathbf{R}_I) \rightarrow k_{IJ} (R_{IJ} - R_{IJ}^0)^2$$

**Molecular mechanics:** empirical functions and parameters describe the energy (e.g., harmonic oscillator for chemical bond)

# Force fields

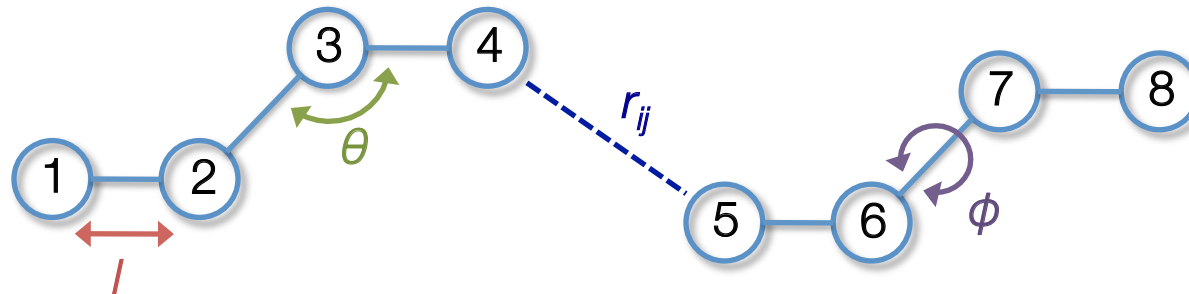


- Force fields are built from *functional forms* and empirical *parameters*
- Interactions include bonded pairwise, 3-body, and 4-body interactions...
- ...as well as non-bonded pairwise interactions
- Simulation accuracy depends critically on parameters

# Force field functional forms (1/3)

- Atoms are spheres of mass  $m_i$ , partial charge  $q_i$ , and van der Waals sort-of-size  $\sigma_i$
- Potential energy function (force field):

$$\begin{aligned}
 U &= U_{\text{bonded}} + U_{\text{non-bonded}} \\
 &= \sum_{\text{bonds}} k_l (l_{ij} - l_{eq})^2 + \sum_{\text{angles}} k_\theta (\theta_{ijk} - \theta_{eq})^2 + \sum_{\text{dihedrals}} V_\phi (1 + \cos(n\phi_{ijkl} - \gamma_n)) \\
 &\quad + \sum_{\text{nonbonded}} \left[ \frac{k_e q_i q_j}{r_{ij}} + 4\epsilon_{ij} \left( \left( \frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left( \frac{\sigma_{ij}}{r_{ij}} \right)^6 \right) \right]
 \end{aligned}$$



# Force field functional forms (2/3)

Non-trivial point #1: the combining/mixing rules for pairwise vdW interactions.

Recap of Lennard-Jones potential for vdW interactions:

$$U_{vdW}(r_{ij}) = \sum_{nonbonded} 4\epsilon_{ij} \left( \left( \sigma_{ij}/r_{ij} \right)^{12} - \left( \sigma_{ij}/r_{ij} \right)^6 \right)$$

Two common mixing rule schemes for these interactions:

$$\left. \begin{array}{l} \epsilon_{ij} = \sqrt{\epsilon_i \epsilon_j} \\ \text{Berthelot} \end{array} \right\} \begin{array}{l} \sigma_{ij} = \frac{1}{2}(\sigma_i + \sigma_j) \text{ Lorentz (e.g., AMBER or CHARMM)} \\ \sigma_{ij} = \sqrt{\sigma_i \sigma_j} \text{ Berthelot, part deux (e.g., OPLS)} \end{array}$$



# Force field functional forms (3/3)

Non-trivial point #2: how to move smoothly from 1-4 interactions to nonbonded interactions.

## Numerous approaches to this problem...

- AMBER/GAFF: scale 1-4 vdW interactions by 0.5; scale 1-4 electrostatic interactions by 0.833
- CHARMM: don't scale 1-4 interactions at all (used to be scale by 0.4)
- OPLS: scale 1-4 interactions by 0.5

# Force field parameterization (1/2)

Force fields are parameterized to compensate for their simplified description of reality.

## **Most models have incomplete physics:**

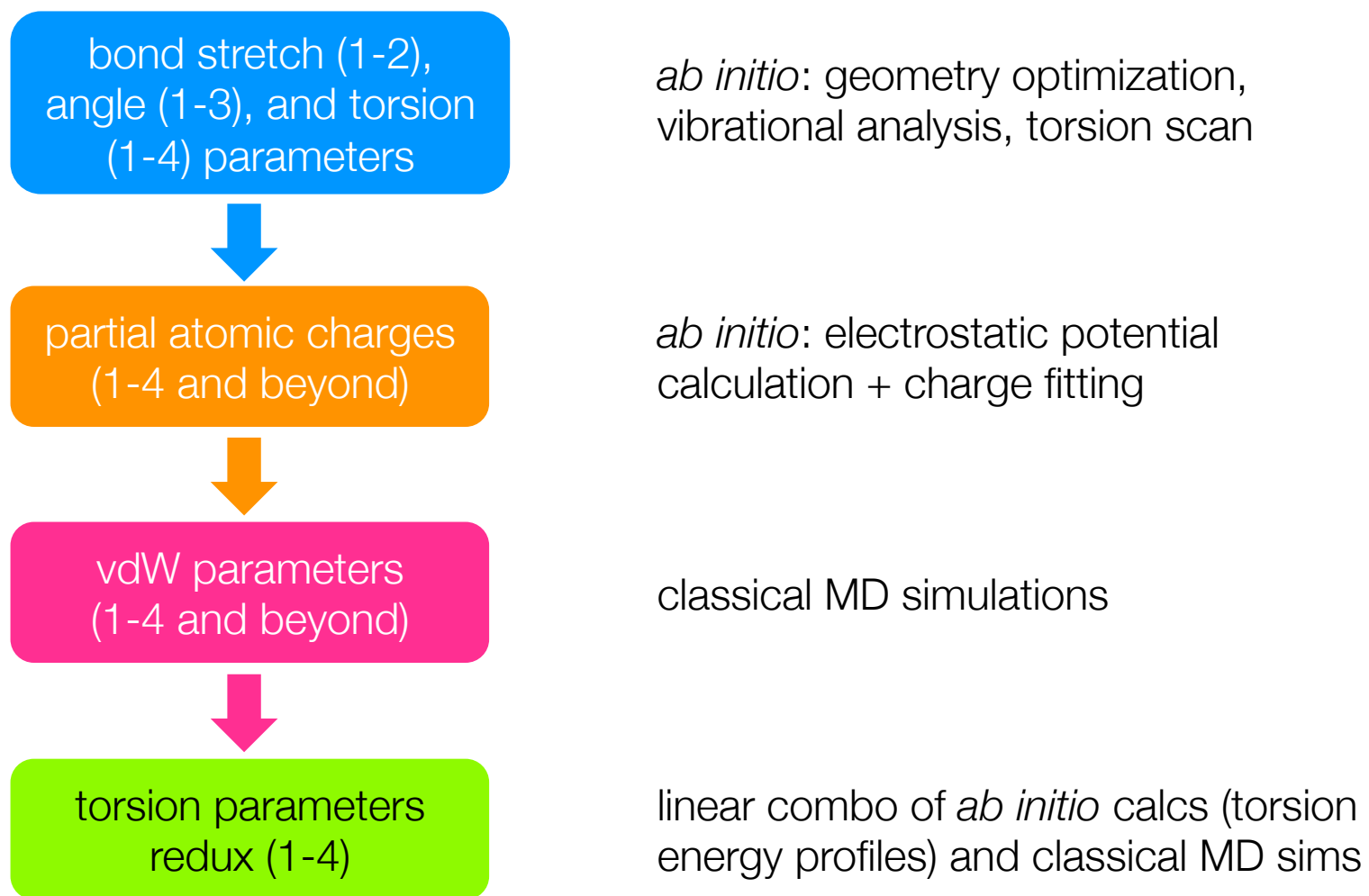
- Fixed point charges (no electronic polarization)
- Classical mechanics (no isotope effects)
- Fixed bond topology (no chemistry)

## **However, much can be recovered through parameterization:**

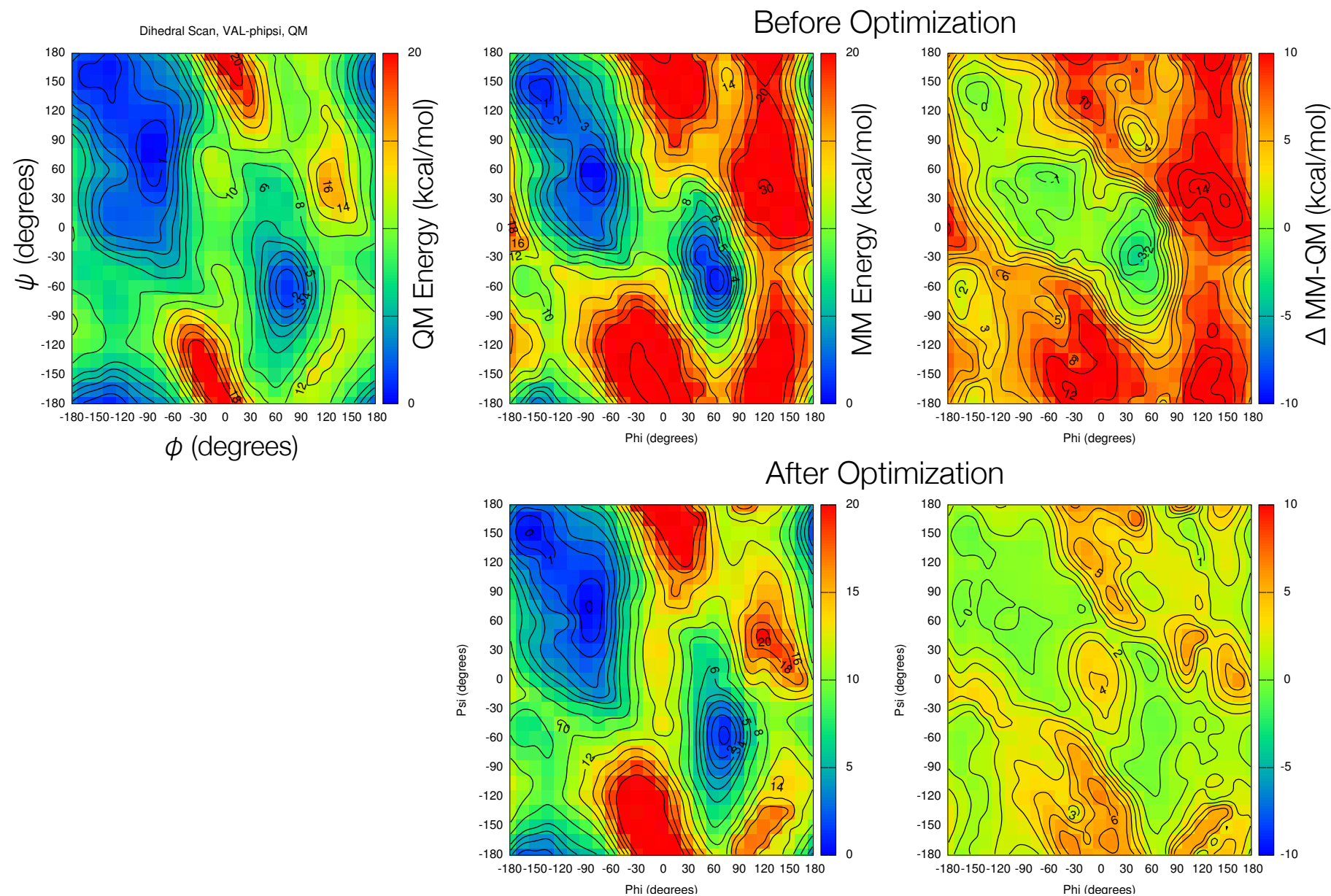
- “Increase” the partial charges to recover polarization effects
- Tune vdW parameters to recover the experimental density
- In many cases, force fields exceed the accuracy of quantum methods!

# Force field parameterization (2/2)

A (typical) force field parameterization flow chart

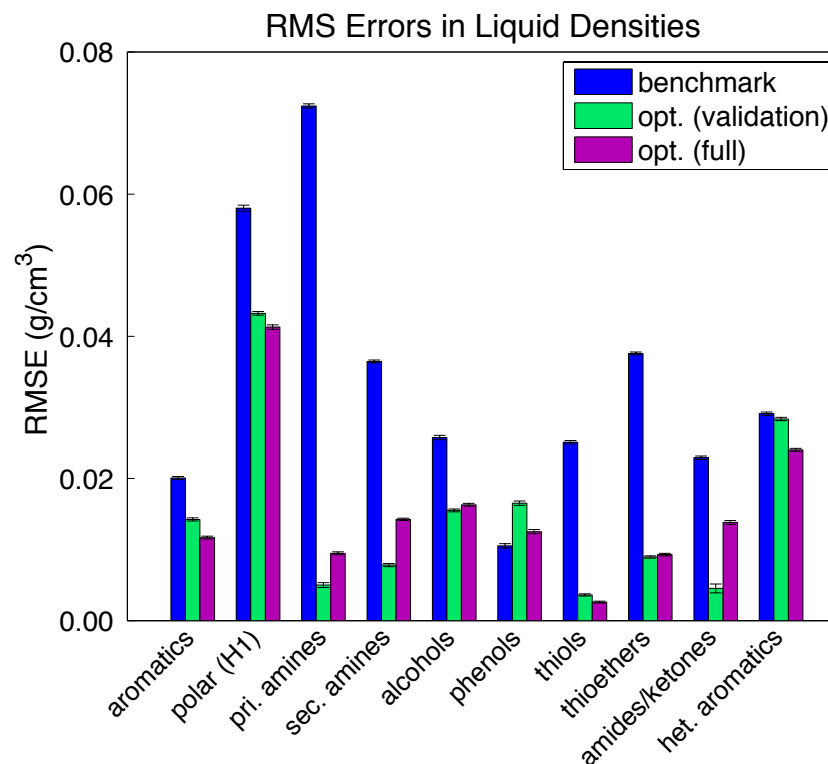
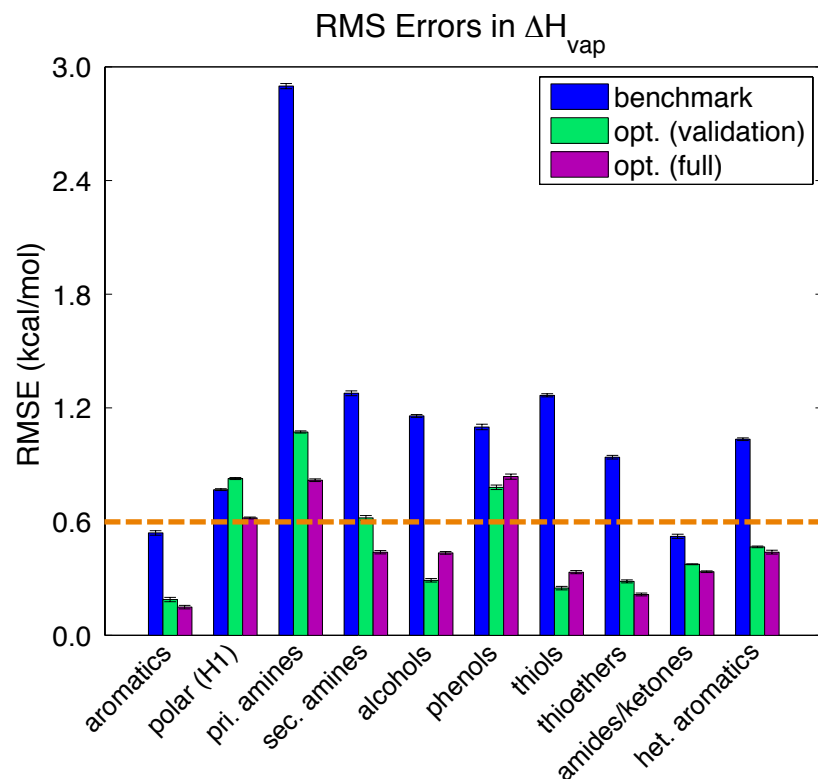


# Fixed-charge FF successes (bonded)



L-P Wang et al. *J Phys Chem B* (2017).

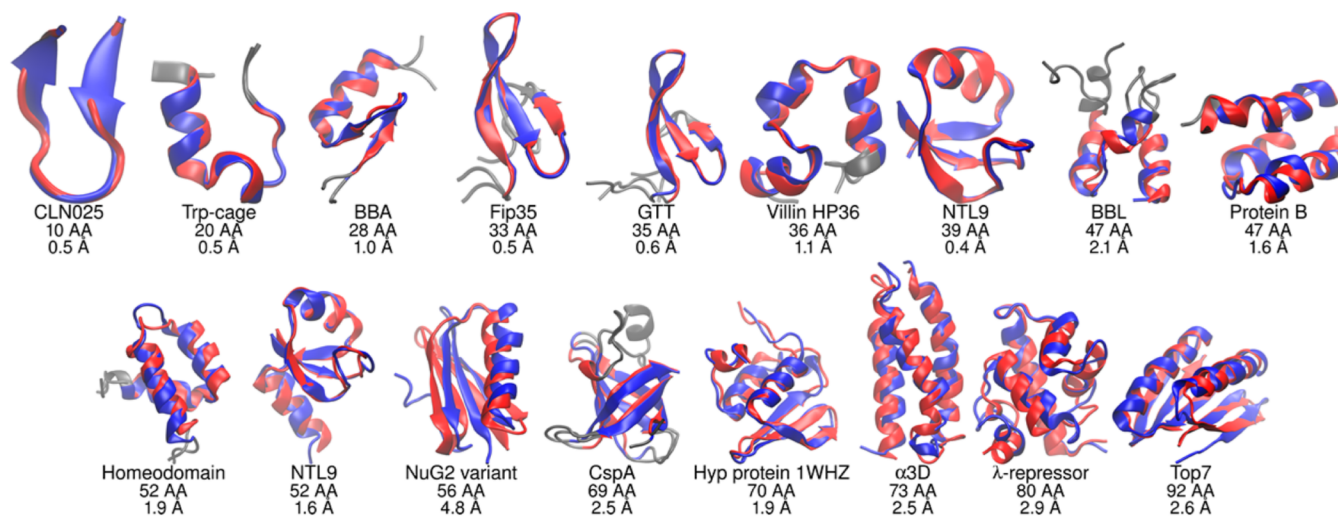
# Fixed-charge FF successes (nonbonded)



# Fixed-charge FF successes (e'rybody)

## Folding Simulations for Proteins with Diverse Topologies Are Accessible in Days with a Physics-Based Force Field and Implicit Solvent

Hai Nguyen,<sup>†,‡,#</sup> James Maier,<sup>‡,§,#</sup> He Huang,<sup>†,‡</sup> Victoria Perrone,<sup>†</sup> and Carlos Simmerling<sup>\*,†,‡,§</sup>



# Conclusions and future directions

- Classical force fields have been able to successfully provide an atomistic description of a wide variety of chemical phenomena
  - Fixed-charge FFs have been (shockingly) useful...  
...but limitations ultimately motivate move to polarizable FFs
- Challenges/opportunities going forward:
  - What physics to include (e.g., polarizability, charge penetration)
  - Functional forms
  - New algorithms to increase **speed** and/or **sampling**
  - Parameterization strategies and data