Introduction to molecular mechanics
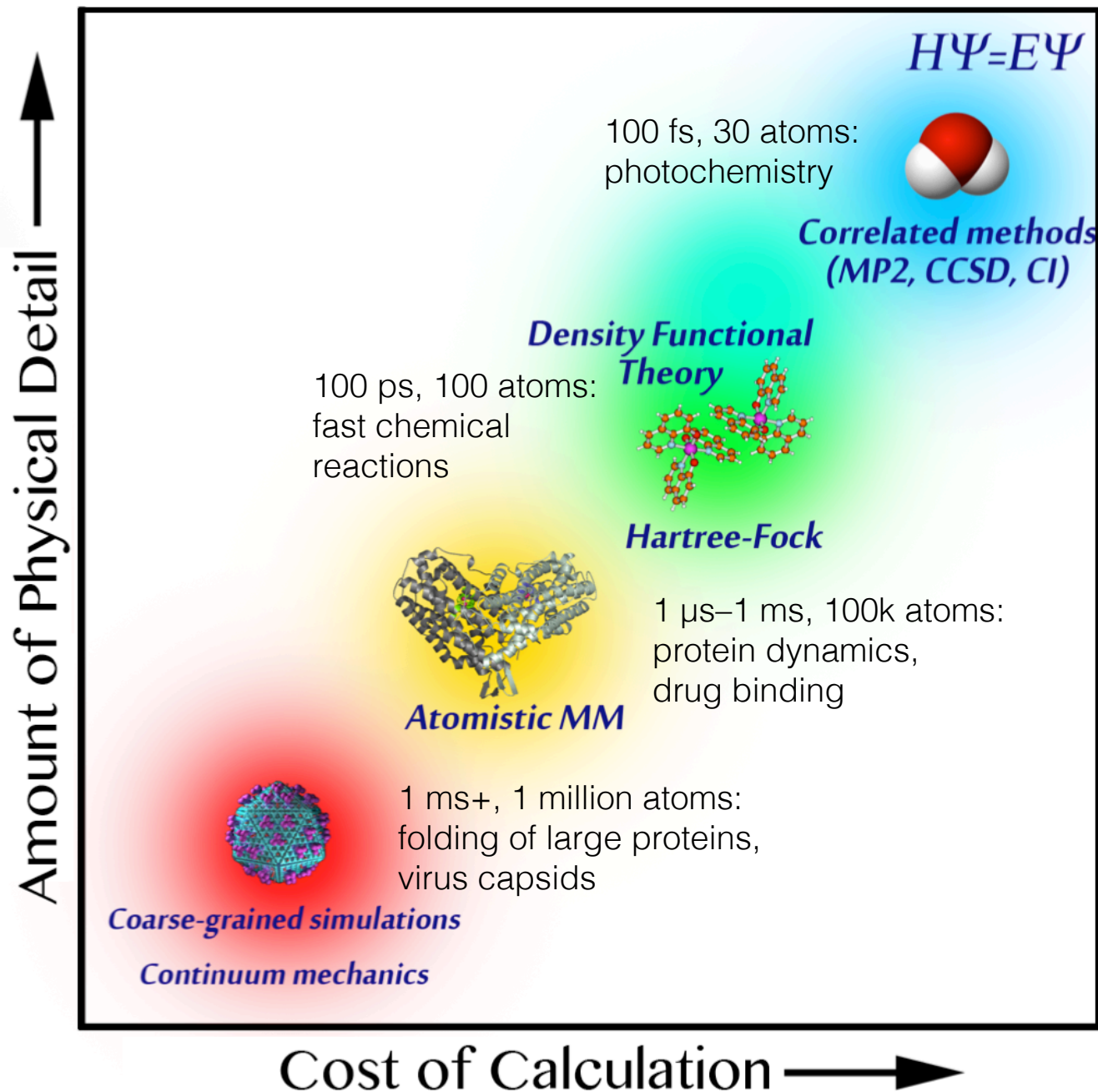
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(+ Lee-Ping Wang)

A bird's eye view of computational chemistry

Amount of Physical Detail →

$H\Psi = E\Psi$

100 fs, 30 atoms: photochemistry

Correlated methods (MP2, CCSD, CI)

Density Functional Theory

100 ps, 100 atoms: fast chemical reactions

Hartree-Fock

1 µs–1 ms, 100k atoms: protein dynamics, drug binding

Atomistic MM

1 ms+, 1 million atoms: folding of large proteins, virus capsids

Coarse-grained simulations

Continuum mechanics

Cost of Calculation →

- 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:

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

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

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

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

Approximate solutions to the SE

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

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

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

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

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

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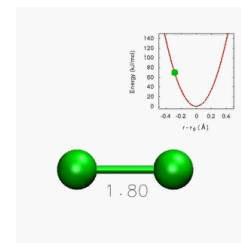
$$E(\mathbf{R}_I) \rightarrow k_{IJ}\left(R_{IJ} - R_{IJ}^0\right)^2$$

Molecular mechanics: empirical functions and parameters describe the energy (e.g., harmonic oscillator for chemical bond)
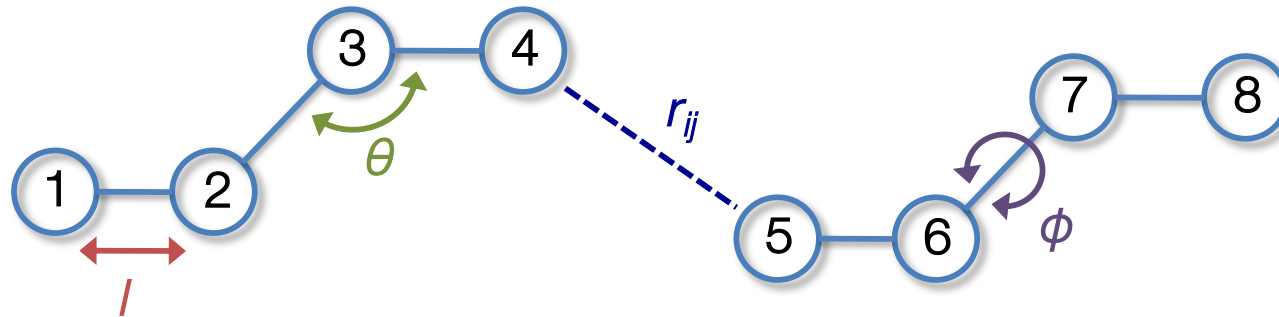
Force fields
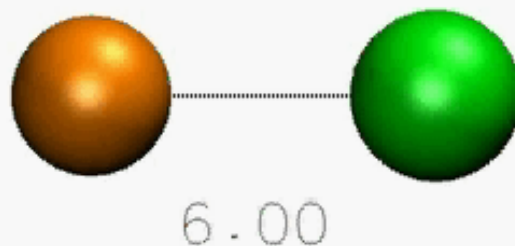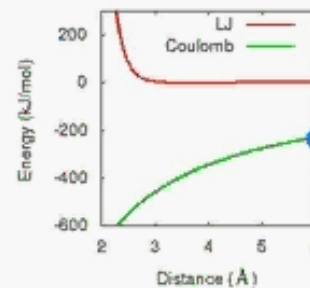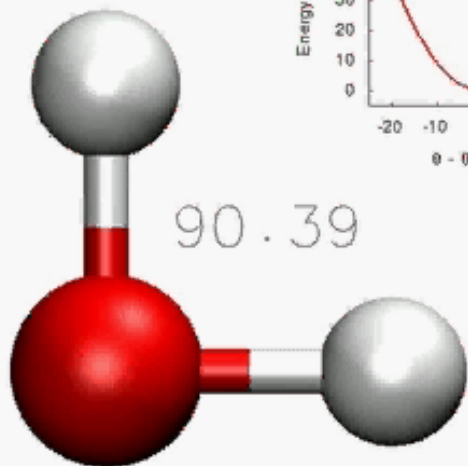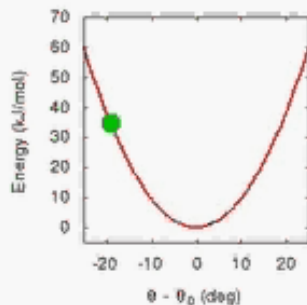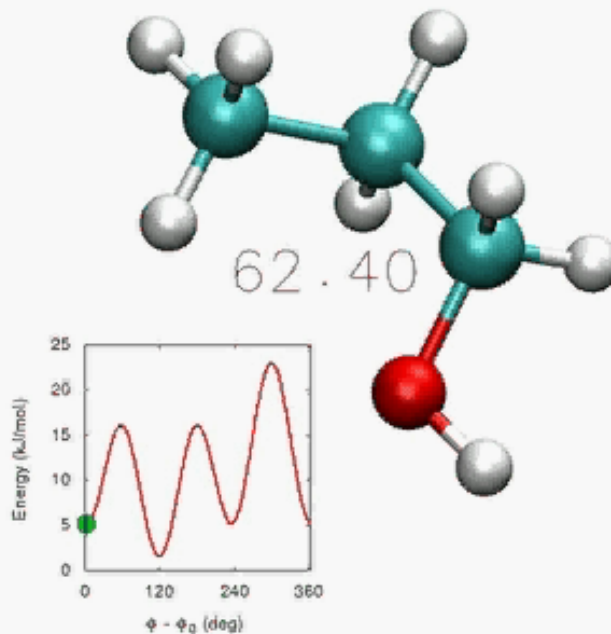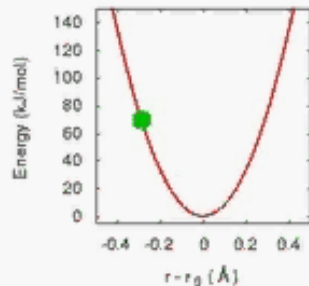
- **Force fields** are built from *functional forms* and empirical *parameters*

- 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 σ_i

- Potential energy function (force field):

$$U = U_{bonded} + U_{non-bonded}$$

$$= \underbrace{\sum_{bonds} k_l \left(l_{ij} - l_{eq} \right)^2}_{} + \underbrace{\sum_{angles} k_\theta \left(\theta_{ijk} - \theta_{eq} \right)^2}_{} + \underbrace{\sum_{dihedrals} V_\phi \left(1 + \cos \left(n\phi_{ijkl} - \gamma_n \right) \right)}_{}$$

$$+ \sum_{nonbonded} \left[\frac{k_e q_i q_j}{r_{ij}} + 4\varepsilon_{ij} \left(\left(\frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}} \right)^6 \right) \right]$$

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:

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

Two common mixing rule schemes for these interactions:

$$\sigma_{ij} = \frac{1}{2}\left(\sigma_i + \sigma_j\right) \quad \text{Lorentz (e.g., AMBER or CHARMM)}$$

$$\varepsilon_{ij} = \sqrt{\varepsilon_i \varepsilon_j}$$

Berthelot

$$\sigma_{ij} = \sqrt{\sigma_i \sigma_j} \quad \text{Berthelot, part deux (e.g., OPLS)}$$

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.

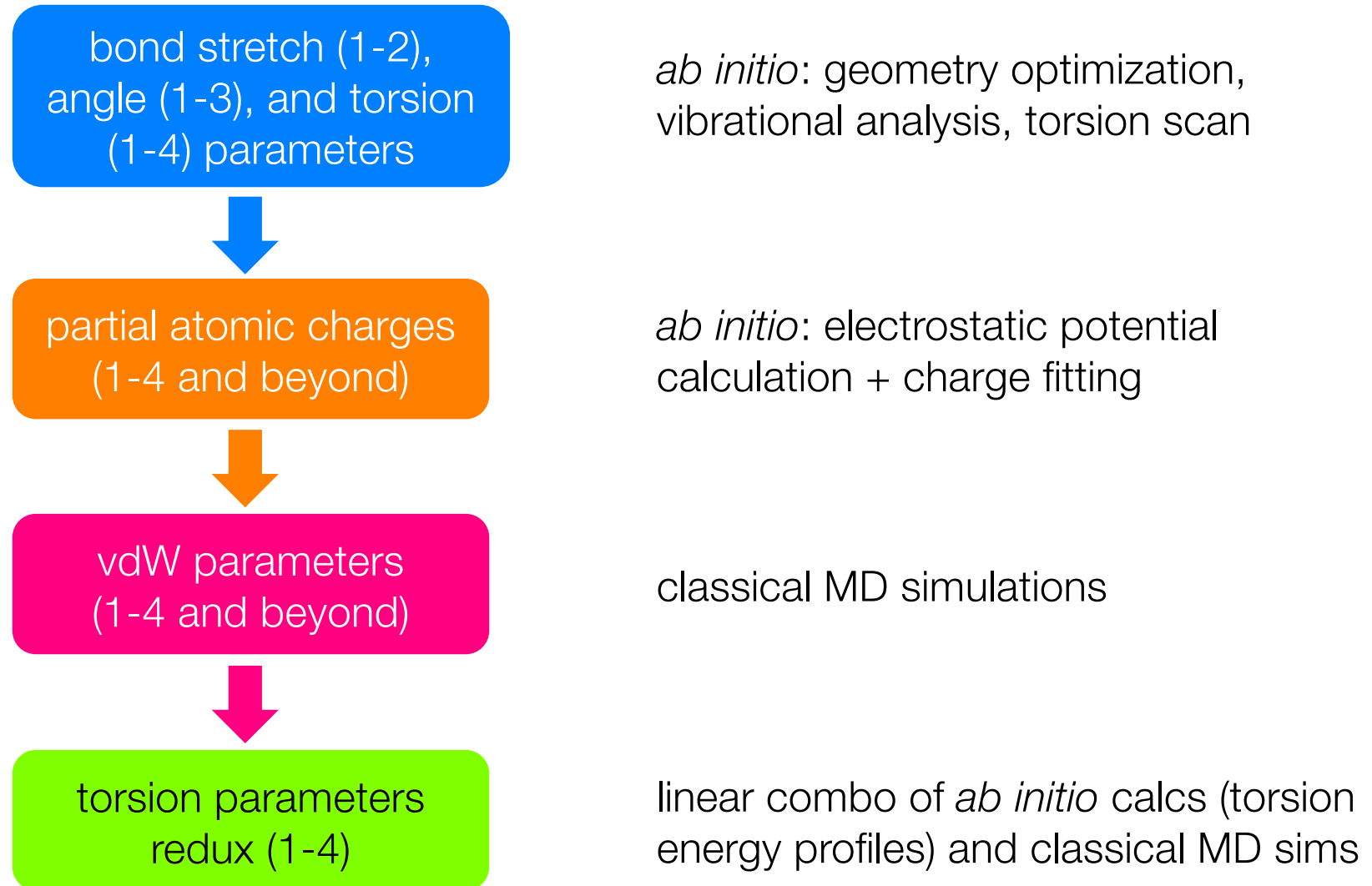**Most models have incomplete physics:**

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

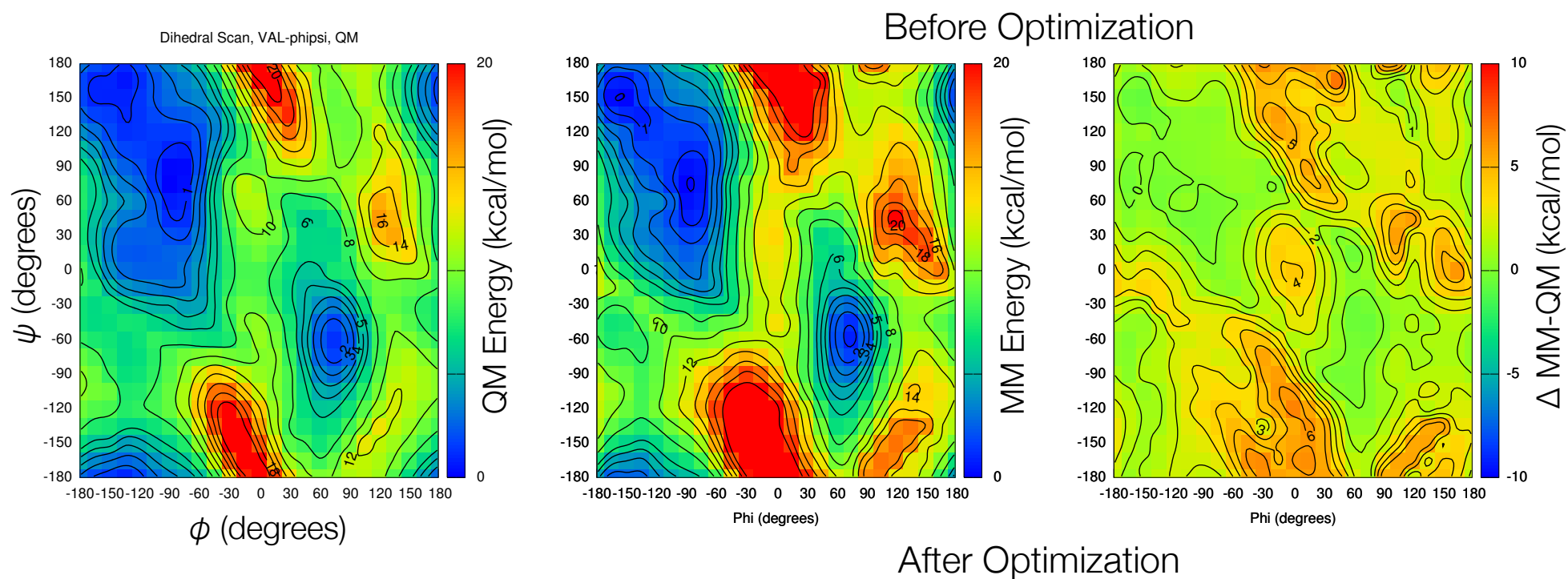**However, much can be recovered through parameterization:**

- "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!
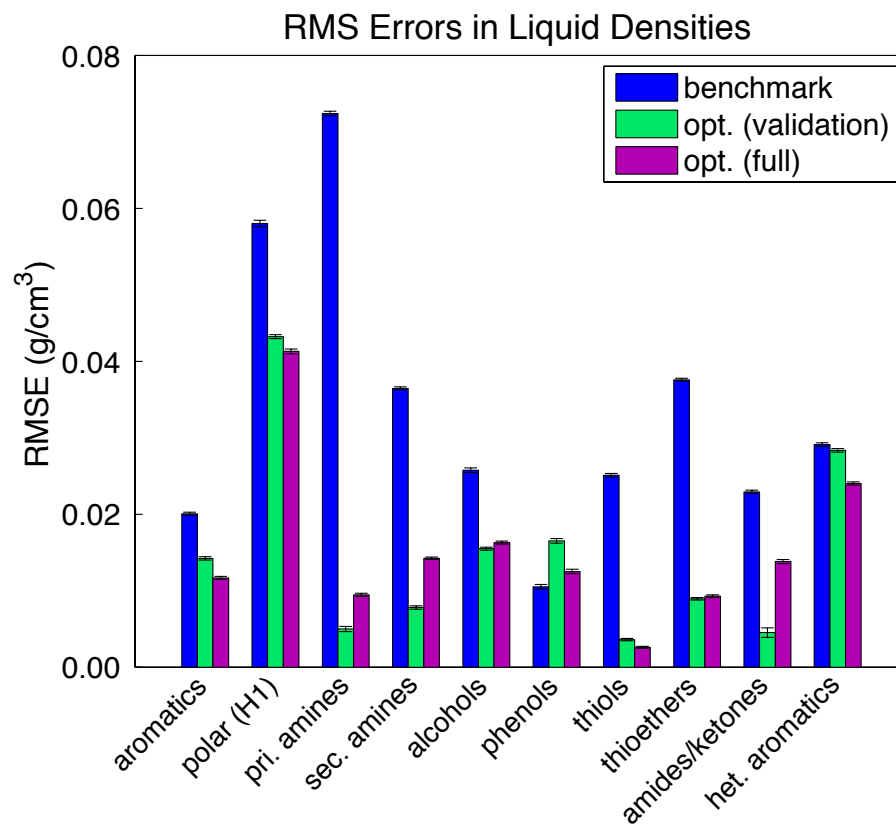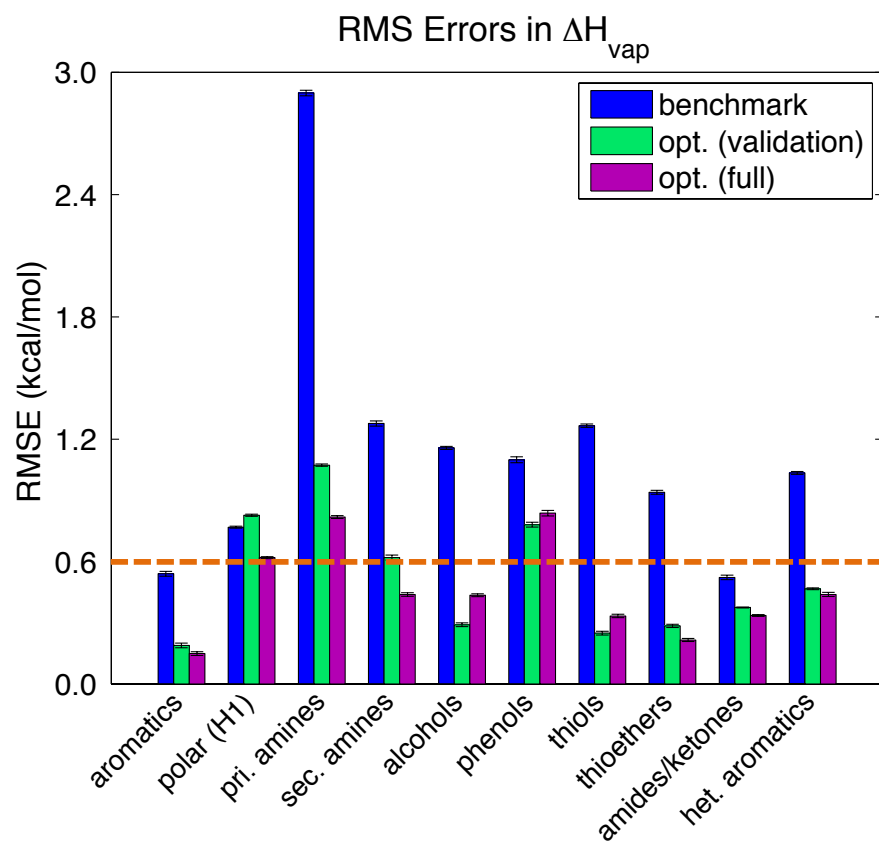
Force field parameterization (2/2)
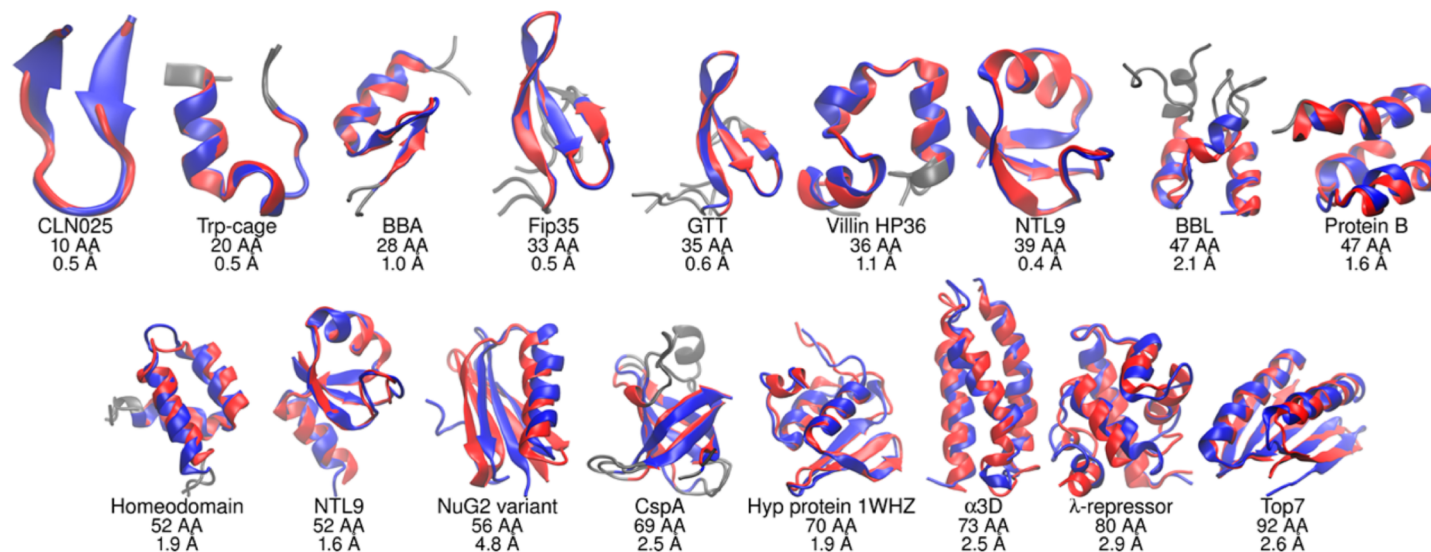
A (typical) force field parameterization flow chart

bond stretch (1-2), angle (1-3), and torsion (1-4) parameters

ab initio: geometry optimization, vibrational analysis, torsion scan

partial atomic charges (1-4 and beyond)

ab initio: electrostatic potential calculation + charge fitting

vdW parameters (1-4 and beyond)

classical MD simulations

torsion parameters redux (1-4)

linear combo of *ab initio* calcs (torsion energy profiles) and classical MD sims

Fixed-charge FF successes (bonded)

Dihedral Scan, VAL-phipsi, QM

After Optimization

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

Fixed-charge FF successes (nonbonded)

DE Chapman, et al. *J Chem Theory Comput* (2014).

Fixed-charge FF successes (all forces)


H Nguyen, et al. *JACS* (2014).

Fixed-charge FF successes (all forces)

Developing a molecular dynamics force field for both folded and disordered protein states

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P Robustelli, et al. *PNAS* (2018).
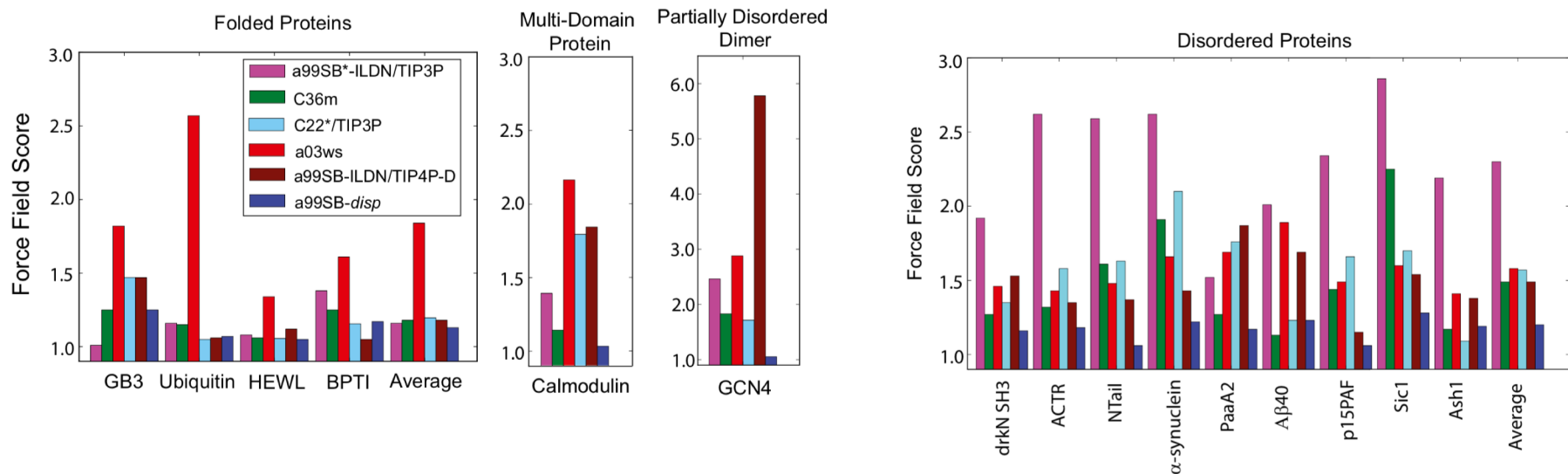
Conclusions and future directions

- 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