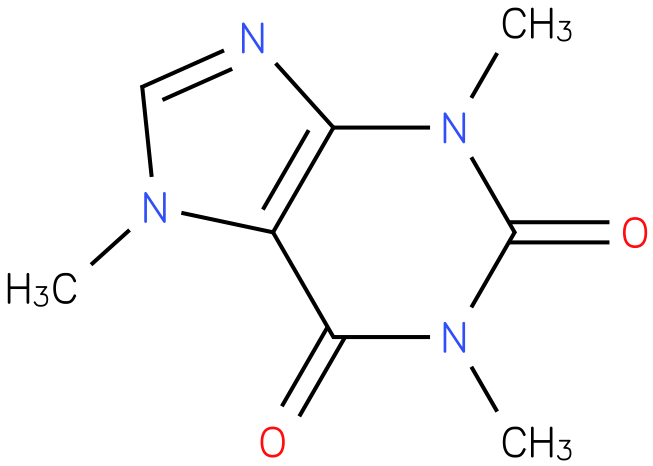
Classical Force Fields

Core concepts

- Atom types: specialisation of elements
- Coefficients: depend on atom types
- Bonds: all bonded pairs (*path of length 1*)
- Angles: two consecutive bonds (*path of length 2*)
- Dihedrals / Torsions: three consecutive bonds
- Improper: dihedral, but not bonded
- Urey-Bradley: Potential on angle end distance

$$
\begin{aligned}
E = &\sum_{\text{bonds}} K_b(b - b_0)^2 + \sum_{\text{angles}} K_\theta(\theta - \theta_0)^2 + \\
&\sum_{\text{dihedrals}} K_\phi\big(1 + \cos(n\phi - \delta)\big) + \\
&\sum_{\text{improper}} K_\varphi(\varphi - \varphi_0)^2 + \\
&\sum_{\text{Urey–Bradley}} K_u(u - u_0)^2 + \\
&\sum_{i<j} 4\varepsilon\left[\left(\frac{\sigma_{ij}}{r_{ij}}\right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}}\right)^{6}\right] + \\
&\sum_{i<j} \frac{q_i q_j}{4\pi\varepsilon_0 r_{ij}}
\end{aligned}
\tag{14}
$$

Let’s find all unique bonds...



Challenges

Fixed, parametric form

- High bias
- Sub-selects chemical space
- Forces topology (even if unstable)

Atom typing

- Non-unique, not automatic
- Often no hard criterion, e.g. for sp^2, sp^3

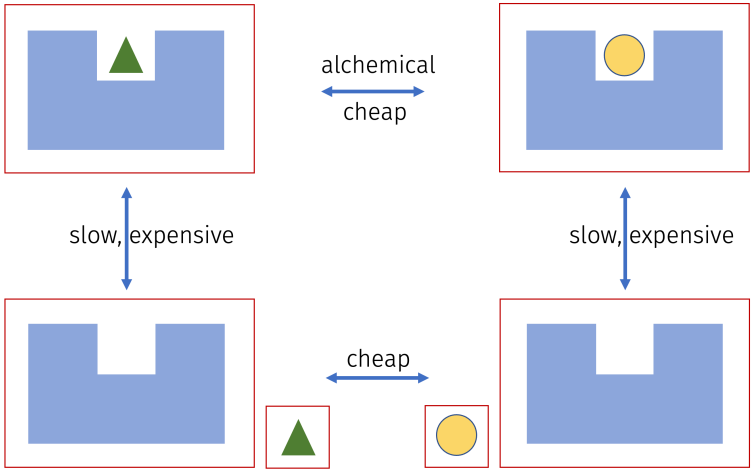
Effort

- New compound, new parametrization: restricts curiosity
- Bias: more of the same much easier than something new

Fitting target

- *DFT*: Hard to match geometries, hardly possible to get ensembles
- *Experiment*: Rarely possible to match both ensemble and geometries

Free energy differences



Close atoms

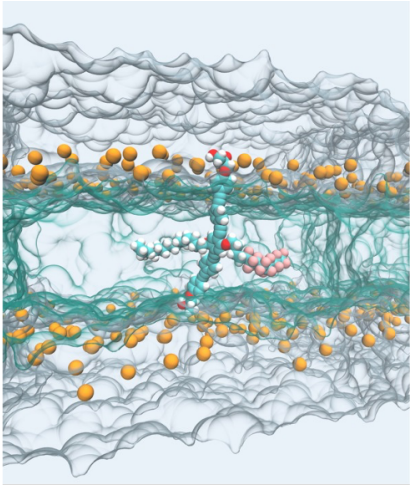
- Insert molecule in membrane: turn on Lennard-Jones potential

distance, minimum position, depth

$$V_{\mathrm{LJ}}(r|\sigma,\varepsilon) = 4\varepsilon\left[\left(\frac{\sigma}{r}\right)^{12} - \left(\frac{\sigma}{r}\right)^{6}\right] \quad (15)$$

Questions

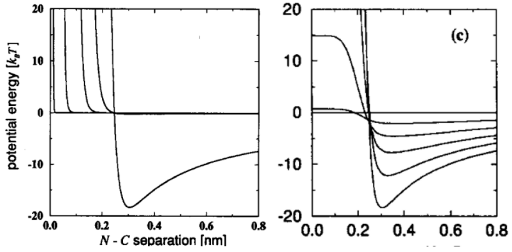
- How to “turn on” interactions?
- Why might that fail?
- What happens if that fails?



https://dx.doi.org/10.1002/jcc.24711

Hard potentials

$$V_{\mathrm{LJ}}(r|\sigma,\varepsilon) = 4\varepsilon\left[\left(\frac{\sigma}{r}\right)^{12} - \left(\frac{\sigma}{r}\right)^{6}\right] \quad (16)$$



∞ Unbounded energy

- no matter the scaling
- no reliable derviatives
- Workaround: soft-core potential U

$$U(r|\sigma,\varepsilon,\lambda) = 4\varepsilon\lambda^n\left[\left(\alpha(1-\lambda)^m + \left(\frac{r}{\sigma}\right)^6\right)^{-2} - \left(\alpha(1-\lambda)^m + \left(\frac{r}{\sigma}\right)6\right)^{-1}\right] \quad (17)$$

T. C. Beutler et al., Chem Phys Lett, *1994*.

Typical molecules:

- effective charges on each site
- Lennard Jones

Transformations

- Can be scaled independently
- Energies remain state function of parameters
- If LJ is scaled: charges can get closer to each other. If charges are of opposite sign: trapping
- Therefore: electrostatics first, LJ second

Question

- Would separate paths be acceptable and if so, why?

Empirical Force Fields for Biological Macromolecules: Overview and Issues

ALEXANDER D. MACKERELL, JR.
Department of Pharmaceutical Sciences, School of Pharmacy, University of Maryland, 20 Penn Street, Baltimore, Maryland 21201

Received 12 April 2004; Accepted 2 May 2004
DOI 10.1002/jcc.20082
Published online in Wiley InterScience (www.interscience.wiley.com).

Abstract: Empirical force field-based studies of biological macromolecules are becoming a common tool for investigating their structure–activity relationships at an atomic level of detail. Such studies facilitate interpretation of experimental data and allow for information not readily accessible to experimental methods to be obtained. A large part of the success of empirical force field-based methods is the quality of the force fields combined with the algorithmic advances that allow for more accurate reproduction of experimental observables. Presented is an overview of the issues associated with the development and application of empirical force fields to biomolecular systems. This is followed by a summary of the force fields commonly applied to the different classes of biomolecules; proteins, nucleic acids, lipids, and carbohydrates. In addition, issues associated with computational studies on "heterogeneous" biomolecular systems and the transferability of force fields to a wide range of organic molecules of pharmacological interest are discussed.

 J Comput Chem 25: 1584–1604, 2004

Key words: molecular dynamics; molecular mechanics; CHARMM; AMBER; OPLS; GROMOS

Classical Force Fields

- Strong approximation with severe bias towards desired outcome
- Not systematically improvable
- Highly subjective approach
- Still relevant for large extended systems, e.g. in biology, since fast and scalable
- For molecular systems: replaced by Machine Learning Force Fields