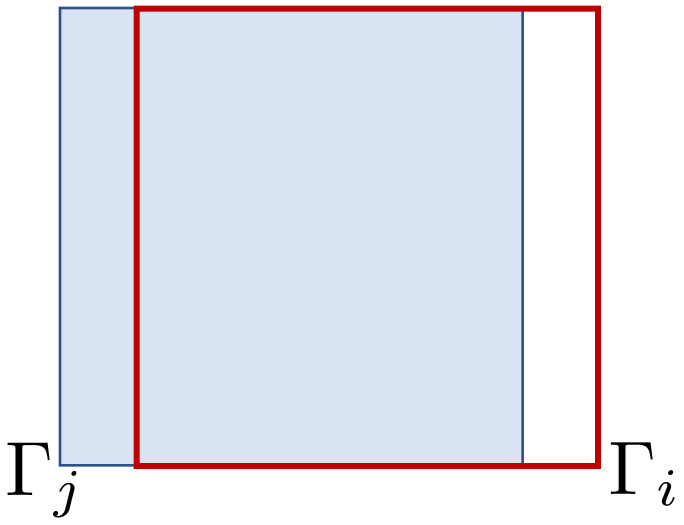
Problem: Phase space overlap

- Two states: i, j
- NVT ensemble



$$Q_i \equiv \int_{\Gamma_i} \exp\left[-\frac{U_i(\vec{q})}{k_B T}\right] d\vec{q}$$

Partition function

Phase space

Potential energy

Example: hard spheres with different radii: close interaction never happens

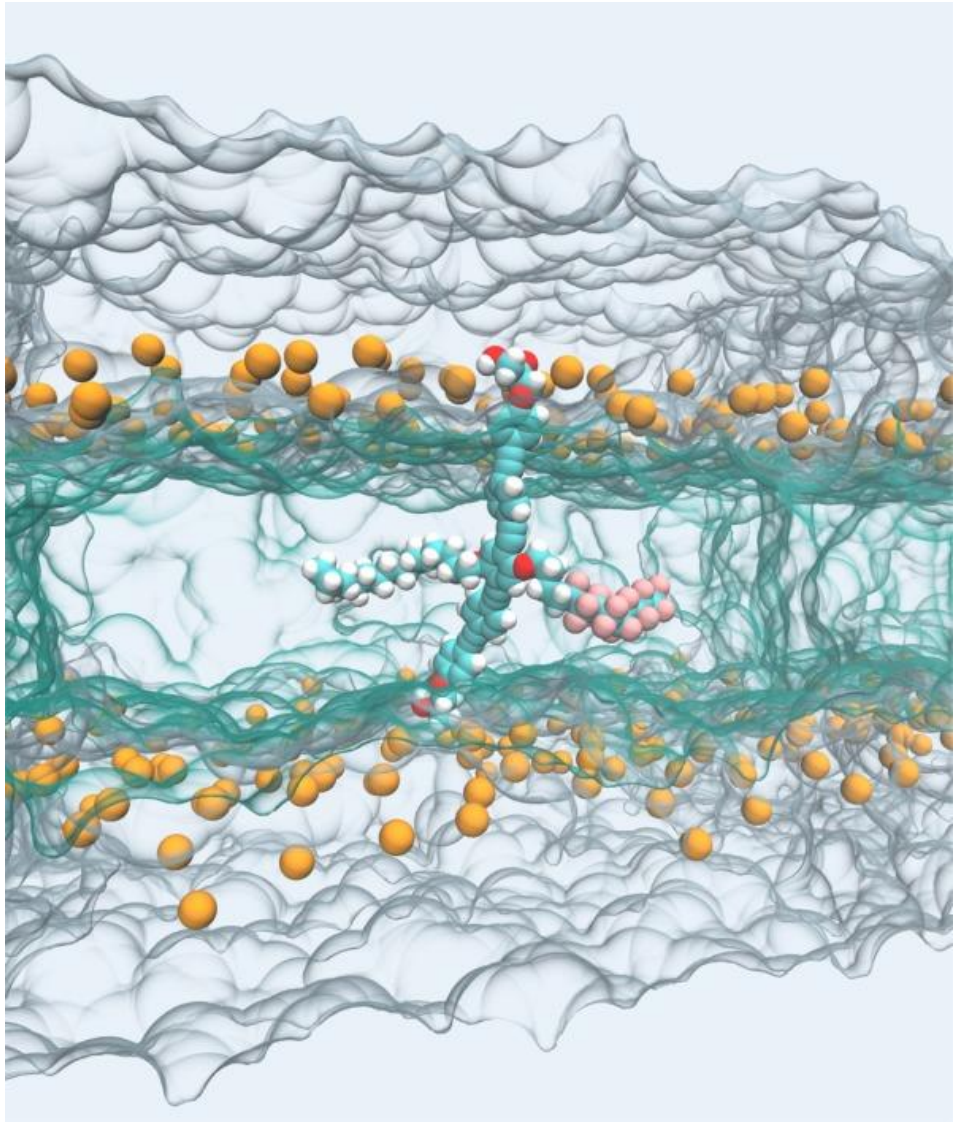
Problem: Singularities

Insert molecule in membrane: turn on interactions

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

Questions:

1. How to “turn on” interactions?
2. Why might that fail?
3. What happens if that fails?



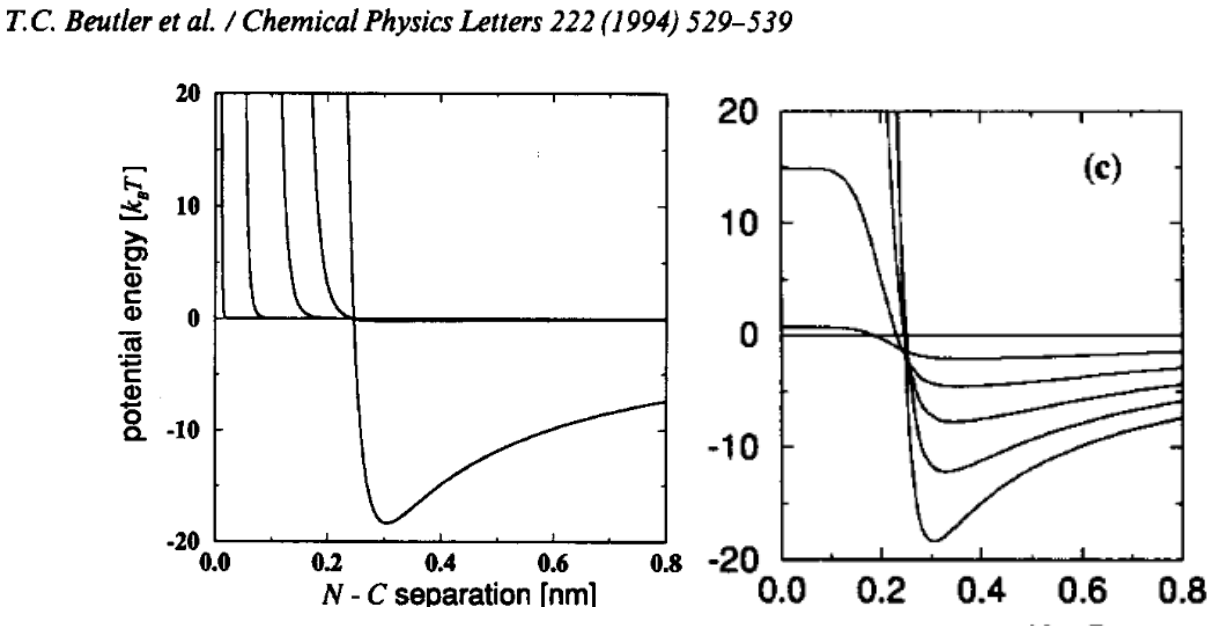
https://dx.doi.org/10.1002/jcc.24711

Problem: Hard potentials

- No matter the scaling: unbounded energy

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

- Unbounded energy: no reliable derivatives
  - Question: Why is that an issue in molecular dynamics?
- Solution: soft-core potentials



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

Problem: Charges and Lennard Jones

- Typical molecules: effective charges on each site + Lennard Jones

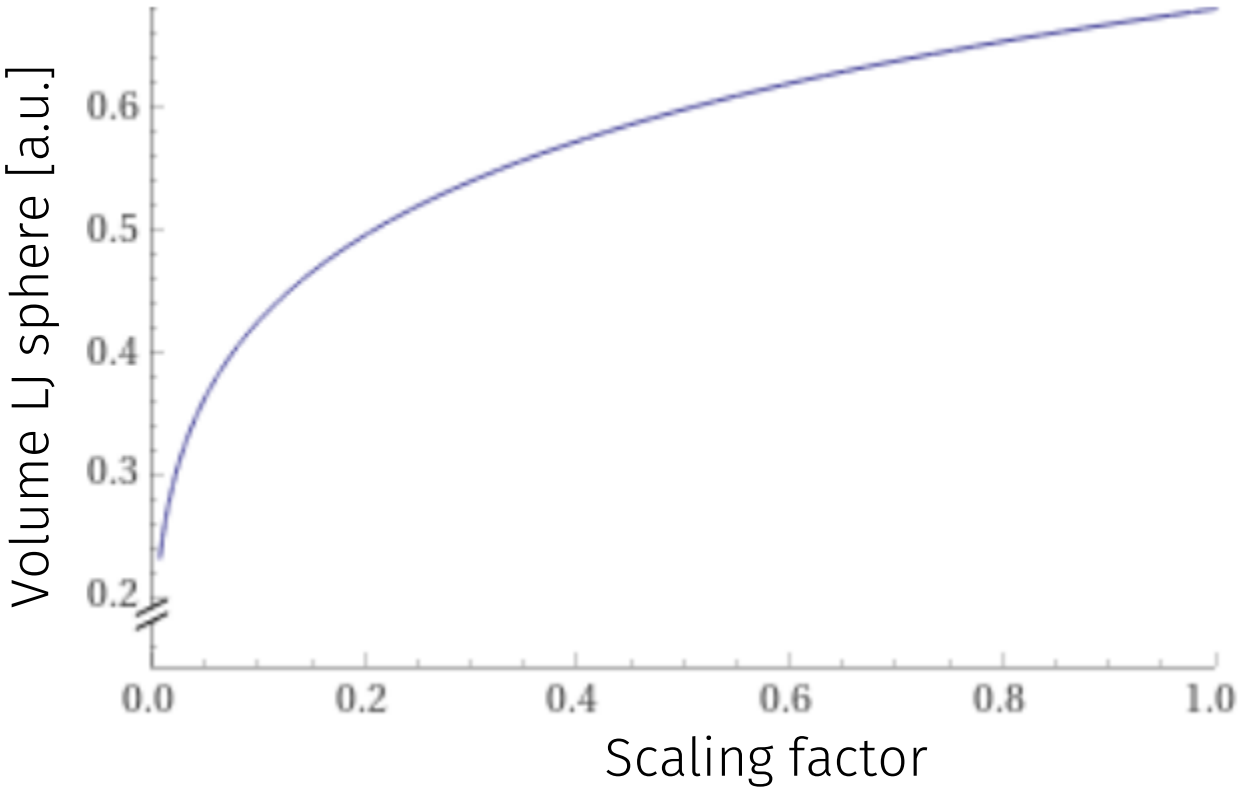
$$V_{\mathrm{LJ}}(r) = 4\varepsilon \left[\left(\frac{\sigma}{r} \right)^{12} - \left(\frac{\sigma}{r} \right)^{6} \right]$$

- Can be scaled independently
  - Energies remain state function of parameters
- Caveat:
  - 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?

Problem: Pathways

Linear pathway not necessarily efficient / rarely “effectively linear”

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

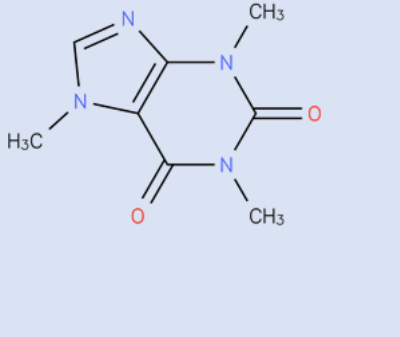


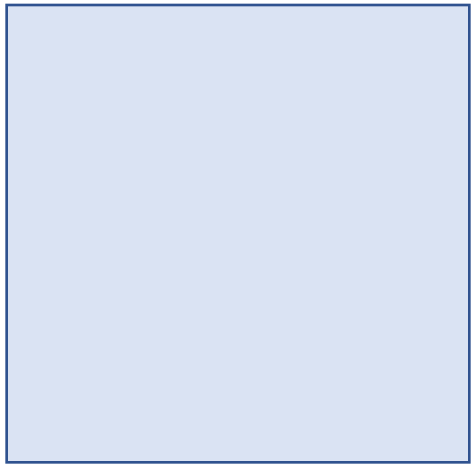
Problem: Pathways

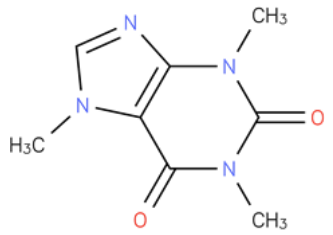
- Avoid constrained/restrained configurations — Why?
- Choose low-change path: large changes mean large derivatives — Why is that bad?
- Change parameters to create effectively linear results
- Restrict number of intermediates (=mixed states)
- Beware electrostatics: keep net charge — Why?

Problem: Pathways

Consider NVT:
Why is the free energy of solvation NOT simply the free energy differences with solute-solvent interactions turned off?







Empirical Force Fields for Biological Macromolecules: Overview and Issues

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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.

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