Classical Use Case:
Alchemical changes

alchemical
cheap

slow, expensive

slow, expensive

cheap
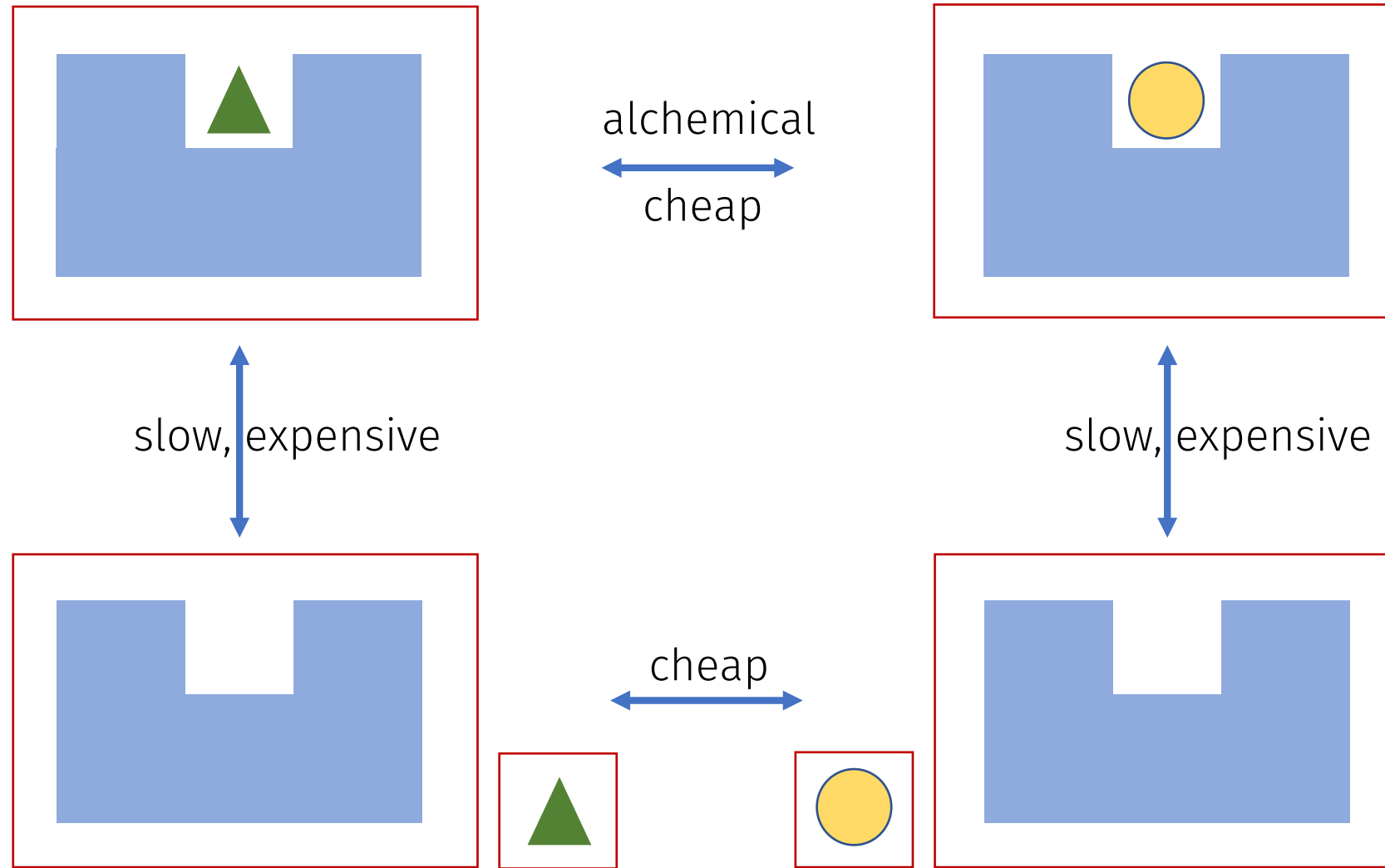
- Two states: i, j
- NVT ensemble, equilibrated

$$\Delta A_{ij} \equiv -k_B T \ln \frac{Q_j}{Q_i}$$

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

Helmholtz free energy

Temperature

Partition function

Phase space

Potential energy

- Need: ensemble average
- Ergodicity: Time average = Ensemble average
- Propagate in small steps (~fs) explicit positions from repeated force evaluations

- Challenges
  - Numerically stable
  - Time reversibility
  - Thermostats / Barostats
  - Equilibration

Questions:
- Why are classical calculations typically time-reversible but quantum mechanical calculations are not?
- What does it mean if a setup is lacking time-reversibility?

- Two states: i, j
- NVT ensemble

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

Γ_j Γ_i
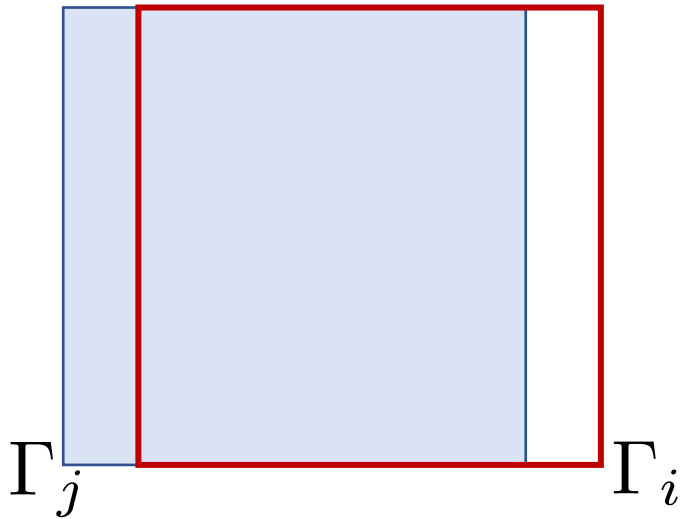
Partition function

Phase space

Potential energy

Example: hard spheres with different radii: close interaction never happens
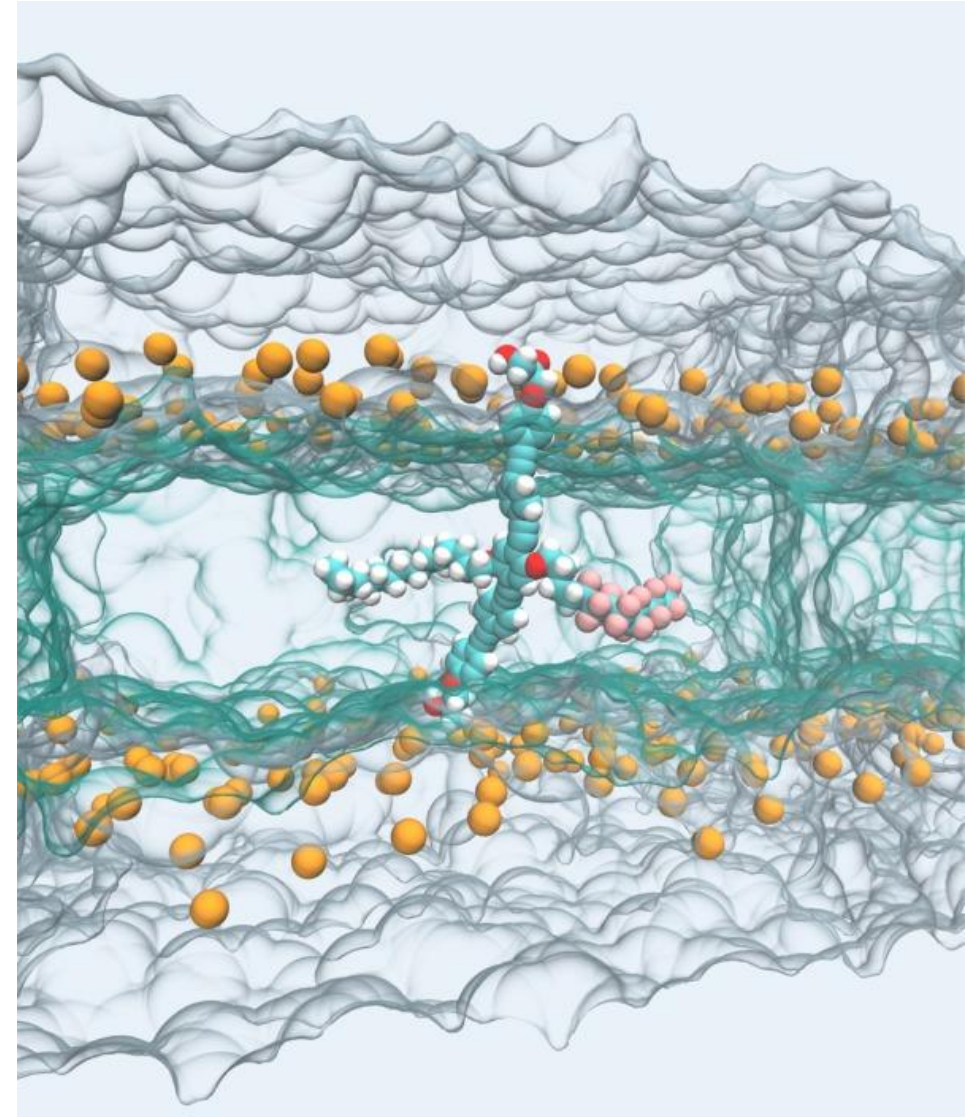
Insert molecule in membrane: turn on interactions

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

Questions:
1. How to "turn on" interactions?
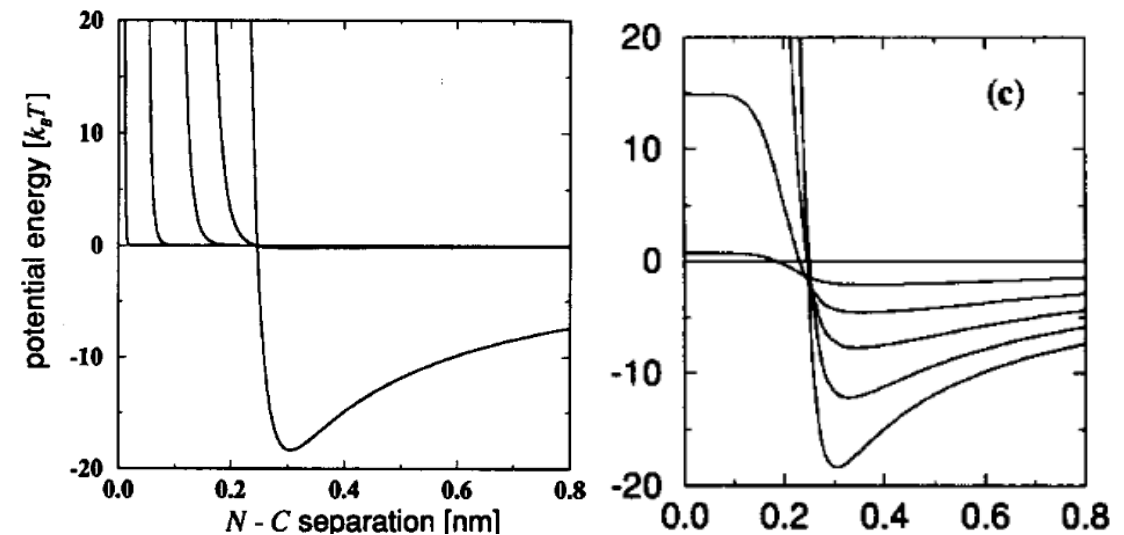2. Why might that fail?
3. What happens if that fails?

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- 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

T.C. Beutler et al. / Chemical Physics Letters 222 (1994) 529–539

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

- 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?