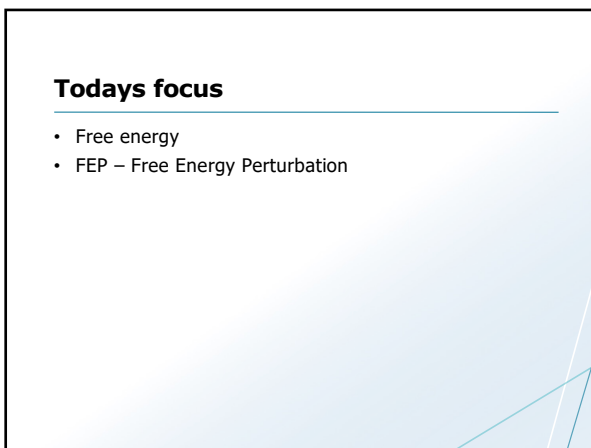
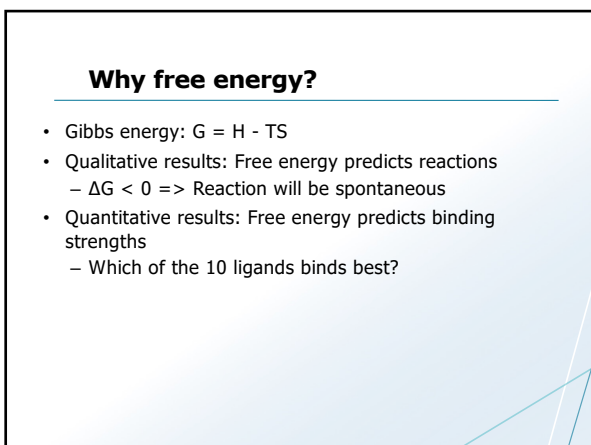


1



2

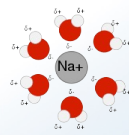


3

Example: Solvation

- Free energy of solvation

Lennard-Jones interactions
between solute and solvent



$$\Delta G_{sol} = \Delta G_{vdw} + \Delta G_{cav} + \Delta G_{elec}$$

Cost for creating cavity in water
(Surface extension / tropy)

Electrostatic
interactions

4

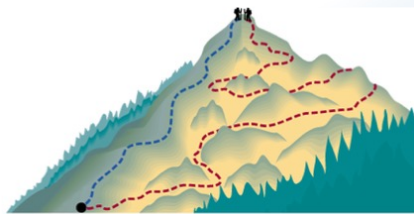
Free energies of biomolecules

- Gibbs free energy G is defined in the NPT ensemble
- Helmholtz free energy H is defined in the NVT ensemble
- Practice - normally to have a pressure-volume work that is zero in biological systems
=> $H = G$

5

Free energy landscape

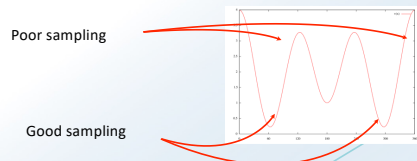
Free energy depend only on the state, not on how we get there



6

The sampling problem

- To get average values we need to sample the entire phase space
- Simulations typically sample low-energy regions
- Large errors due to poor sampling of high-energy regions



7

Absolute free energy

- Very difficult to obtain from simulations - entropy is a problem
- Sometimes possible to estimate
 - Cavity sizes in water when solvating ions can be calculated
 - Loss of entropy when a bond cannot rotate anymore can be approximated
- Normally we do not need absolute energies

8

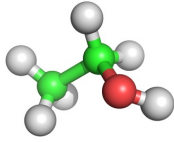
Relative free energies

- What is the difference in free energy when binding a sodium ion vs potassium ion here?
- Alternative formulation for binding:
 - What is the difference between having this ligand in water and having it bound in the receptor?
- Compare different system setups

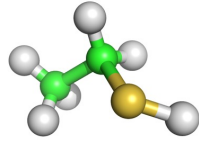
9

Computational alchemy

- Literally means "the art of transforming"



Ethanol



Ethane thiol

- Same "coordinates" but different interactions

10

Free energy perturbation (FEP)

- Let us consider two systems A and B described by U_A and U_B :

$$F = -kT \ln Q = \int \dots \int e^{-U_{pot}/kT} d\vec{r}_1 \dots d\vec{r}_N / \Lambda^{3N}$$

$$\Delta F = -kT \ln \frac{Q_B}{Q_A}$$

$$= -kT \ln \frac{Z_B}{Z_A} = -kT \ln \frac{\int e^{-U_B/kT} d\Gamma}{\int e^{-U_A/kT} d\Gamma}$$

Configurational integral, Z

11

Free energy perturbation (FEP)

$$\Delta F = -kT \ln \frac{\int e^{-U_B/kT} e^{+U_A/kT} e^{-U_A/kT} d\Gamma}{\int e^{-U_A/kT} d\Gamma}$$

$$= -kT \ln \frac{\int e^{-(U_B-U_A)} e^{-U_A/kT} d\Gamma}{\int e^{-U_A/kT} d\Gamma}$$

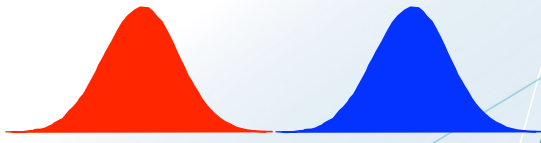
$$= -kT \ln \left\langle e^{-(U_B-U_A)/kT} \right\rangle_A$$

FEP
(Zwanzig's formula)

12

Free energy perturbation (FEP)

- We must have reasonable overlap between the two phase spaces
- Similar states should be favored
- Otherwise we get an average of extremely large positive/negative values and low accuracy



13

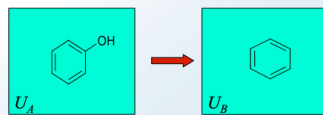
Free energy perturbation (FEP)

Fixing the sampling issue:

- introduce artificial intermediate states described by

$$U_m = (1 - \lambda_m)U_A + \lambda_m U_B = U_A + \lambda_m \Delta U$$

$$\Delta U = U_B - U_A$$



14

Free energy perturbation (FEP)

$$U_m = (1 - \lambda_m)U_A + \lambda_m U_B = U_A + \lambda_m \Delta U$$

$$\Delta G = G_B - G_A = -\beta^{-1} \ln \langle \exp(-\beta \Delta U) \rangle_A$$

$$\Delta U = U_B - U_A$$

$$\Delta G = G_B - G_A = -\beta^{-1} \sum_{m=1}^{p-1} \ln \langle \exp[-\beta(U_{m+1} - U_m)] \rangle_m$$

15

Thermodynamic integration

- Let $U(\lambda = 0) = U_A$ and $U(\lambda = 1) = U_B$:

$$\Delta F = \int_0^1 \frac{\partial F}{\partial \lambda} d\lambda$$

$$\frac{\partial F(\lambda)}{\partial \lambda} = -kT \frac{\partial \ln Z(\lambda)}{\partial \lambda} = -kT \frac{1}{Z} \frac{\partial Z(\lambda)}{\partial \lambda}$$

$$= -kT \frac{1}{Z} \frac{\partial}{\partial \lambda} \int e^{-U(\lambda)/kT} d\Gamma = \frac{\int \frac{\partial U(\lambda)}{\partial \lambda} e^{-U(\lambda)/kT} d\Gamma}{\int e^{-U(\lambda)/kT} d\Gamma}$$

16

Thermodynamic integration

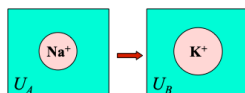
$$\frac{\partial F(\lambda)}{\partial \lambda} = \left\langle \frac{\partial U(\lambda)}{\partial \lambda} \right\rangle_\lambda \quad \text{Calculated from MD simulations}$$

$$\Delta F = \int_0^1 \frac{\partial F}{\partial \lambda} d\lambda = \int_0^1 \left\langle \frac{\partial U}{\partial \lambda} \right\rangle_\lambda d\lambda$$

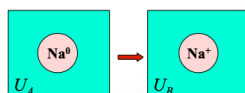
TI (integration formula)

17

Example of vdW and charge transformations

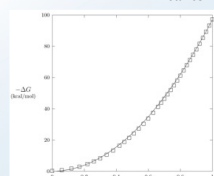
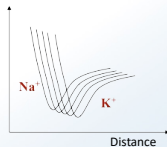


$$\Delta U = U_{K^+}^{IJ} - U_{Na^+}^{IJ}$$



$$\Delta U = U_{Na^+}^{el}$$

Ion-water LJ energy



18

FEP is actually equivalent to TI

- Requires close λ -spacing

$$\Delta G = G_B - G_A = -\beta^{-1} \sum_{m=1}^{n-1} \ln \left\langle \exp \left[-\beta (U_{m+1} - U_m) \right] \right\rangle_m$$

$$\Delta G = -\beta^{-1} \sum_{m=1}^{n-1} \ln \left\langle \exp \left[-\beta \Delta U \Delta \lambda_m \right] \right\rangle_m$$

$$\Delta G = -\beta^{-1} \sum_{m=1}^{n-1} \ln \left\langle \exp \left[-\beta \frac{\partial U_m}{\partial \lambda_m} \Delta \lambda_m \right] \right\rangle_m$$

$$\Delta G = \sum_{m=1}^{n-1} \left\langle \frac{\partial U_m}{\partial \lambda_m} \right\rangle_m \Delta \lambda_m$$

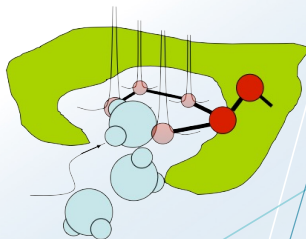
$$\Delta G = \int_0^1 \left\langle \frac{\partial U(\lambda)}{\partial \lambda} \right\rangle_\lambda d\lambda$$

$$\begin{aligned} \Delta U &= U_B - U_A \\ U_m &= (1 - \lambda_m) U_A + \lambda_m U_B \\ \Delta \lambda_m &= \lambda_{m+1} - \lambda_m \end{aligned}$$

19

Practical problems with FEP/TI

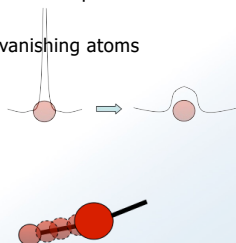
- Appearing or vanishing atoms
- Numerical problems with infinite energies (and forces in MD)
- Sampling problem - "pin-ball" effect
- Timescale problem with large conformational changes



20

How to deal with these problems?

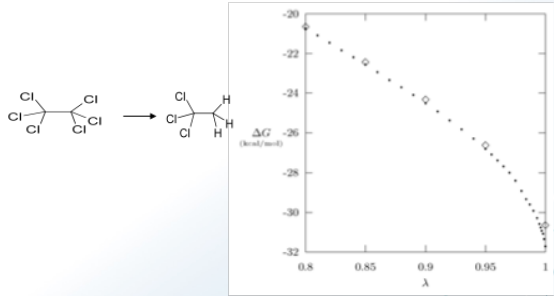
- Transform Lennard-Jones potential into a softer potential
- Shrink bonds to vanishing atoms



21

How to deal with these problems?

- Use a denser λ - spacing near end-points



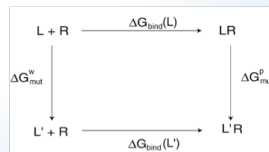
22

FEP/TI and ligand binding

Thermodynamic cycle approach

$$\Delta G = \int_0^1 \left\langle \frac{\partial U(\lambda)}{\partial \lambda} \right\rangle_\lambda d\lambda$$

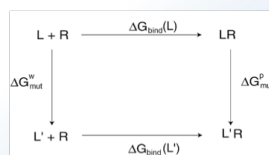
$$\Delta G = G_B - G_A = -\beta^{-1} \sum_{m=1}^{n-1} \ln \left\langle \exp \left[-\beta (U_{m+1} - U_m) \right] \right\rangle_m$$



23

FEP/TI and ligand binding

Thermodynamic cycle approach

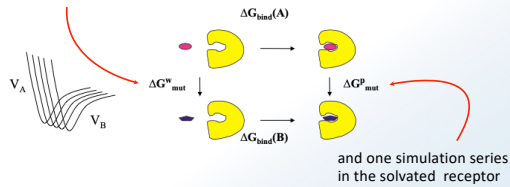


$$\Delta \Delta G_{bind} = \Delta G_{bind}(L') - \Delta G_{bind}(L) = \Delta G_{mut}^p - \Delta G_{mut}^w$$

24

FEP/TI and ligand binding

One simulation series in water



$$\Delta\Delta G_{bind} = \Delta G_{bind}(L') - \Delta G_{bind}(L) = \Delta G_{mut}^p - \Delta G_{mut}^w$$

25

Improving TI

- Start N simulations at separate λ - values
- Calculate $\partial G / \partial \lambda$ from each
- Approximate integral with a sum
- Typically 10-20 values are used

26

Potential of mean force

- Sometimes free energies correspond to closely to a physical process, for instance pulling a ligand out of a binding pocket or bringing a side-chain into a membrane
- Instead of measuring G directly, we can compute the work required to accomplish the change (work = force x distance)
- Potential of mean force

27

Barrier problem

- If we pull a side-chain, it will cross barriers very quickly giving rise to bad sampling
- How can we achieve good sampling in the high energy regions?
- We force the particles to stay there!
- Umbrella sampling

28

Umbrella sampling

- Modify the interaction with a **biasing potential** W :
 $V'=V+W$
- Set the biasing potential to "cancel" the barrier, so that the net free energy will be low there
- Typically accomplished with harmonic potentials
- An umbrella potential will affect sampling
 - We can adjust the final free energy for the basis

29

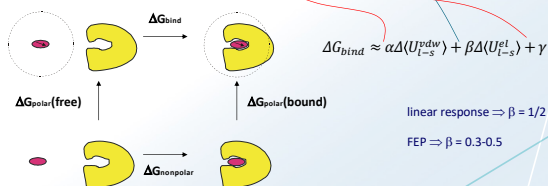
The Linear Interaction Energy (LIE) method

Can we estimate ΔG_{bind} from simulations of the two physical states (bound and free) only?

- $\Delta G_{bind} = \Delta G_{polar} + \Delta G_{nonpolar}$

- ΔG_{polar} from electrostatic linear response

- $\Delta G_{nonpolar}$ from empirical relationships



34
