DUE ON TUES 4 APRIL

LECTURE 12: STATISTICAL MECHANICS

SUMMARY OF LAST TIME

$\rho(\vec{x}) = \dfrac{e^{-E(\vec{x})/k_BT}}{\int d\vec{x}' e^{-E(\vec{x}')/k_BT}}$

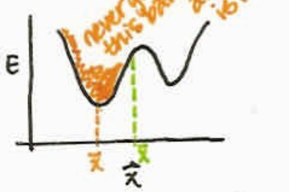
denominator $= Q$ (configurational partition function)

- Uniform Sampling

$\overline{f(\vec{x})} = \langle f(\vec{x}) \rangle = \int d\vec{x}\, \rho(\vec{x}) f(\vec{x})$ (ρ: probability; f: desired function)

- Boltzman Sampling
  Molecular Dynamics or
  Metropolis Monte Carlo Simulation

$\langle f(\vec{x}) \rangle = \frac{1}{M} \sum_{i=1}^{M} f(\vec{x}_i)$



Problem: Free Energy doesn't exist in single frame
~~$f(\vec{x}) \leftarrow A(\vec{x})$~~ so can't compute this way

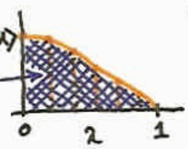
Solution: Can compute free energy changes from simulation (ensemble) averages

$A = -k_BT \ln Q$

If $U(\lambda) = (1-\lambda)U_0 + \lambda U_1$ and let $\Delta U = U_1 - U_0$

$\Delta U(\vec{x}) = U_1(\vec{x}) - U_0(\vec{x})$

Then $\Delta A = A_1 - A_0 = \int_0^1 d\lambda \langle \Delta U \rangle_\lambda$

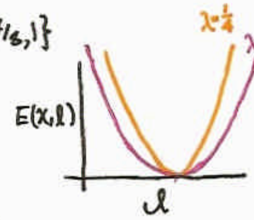


Run a series of simulations with

$U(\lambda) = (1-\lambda)U_0 + \lambda U_1$
$= \frac{1}{2}(1-\lambda)k_0(x-l)^2 + \frac{1}{2}\lambda k_1 (x-l)^2$
$= \frac{1}{2}[k_0 + \lambda(k_1 - k_0)](x-l)^2$

$\lambda = \{0, 1/8, 1/4, 3/8, 1/2, 5/8, 3/4, 7/8, 1\}$

$\Delta U = \frac{1}{2}(k_1 - k_0)(x-l)^2$

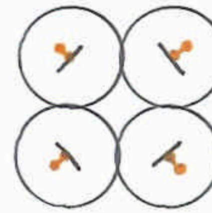


$\Delta U = U_1 - U_0 = \sum_i \Delta U_i$

$\Delta A = \int_0^1 d\lambda \langle \Delta U \rangle = \int_0^1 d\lambda \langle \sum_i \Delta U_i \rangle = \sum_i \underbrace{\int_0^1 d\lambda \langle \Delta U_i \rangle}_{\Delta A_i} = \sum_i \Delta A_i$

Science, 244:1069-1072 (1989)

Hemoglobin



ALLOSTERIC PROTEIN WHICH BINDS OXYGEN

ΔA_{al} ← al for "allosteric"

wild type: DEOXY ⇌ OXY
(low O_2 affinity) (high O_2 affinity)

mutant: DEOXY′ ⇌ OXY′ ← Hb Radcliffe mutation [hemoglobin]
(ΔA_{deoxy}, $\Delta A'_{al}$, ΔA_{oxy})

Asp G1(99)β → Ala
(⊖ → ⊙)

Experimentally:

$\Delta\Delta A = \Delta A' - \Delta A = -3.4$ kcal/mol/interface

- Reduced cooperativity & increased oxygen affinity
- Shifts equilibrium toward Oxy′
- Less ability to release O_2 at muscles

DEOXY (wild type): ~~Asp~~ (Ala) 99β ||||||| h-bond Tyr C7(42)α; |||||| Asn G4(97)α

OXY: Asp99β⊖ |||||| solvent;)))(((Asp94α⊖; Tyr42α; Asn97α

thermodynamic cycle → $0 = \Delta A_{deoxy} + \Delta A'_{al} - \Delta A_{oxy} - \Delta A_{al}$

$\Delta\Delta A = \Delta A'_{al} - \Delta A_{al} = \Delta A_{oxy} - \Delta A_{deoxy}$

$\Delta\Delta A_{calc} = -5.5$ kcal/mol/interface

	ΔΔA [kcal/mol/interface]	
Total	-5.5	
Solvent	+22.5	← Ⓐ Strong solvation in oxy state
• Tyr42α	-12.7	← Ⓒ consistent w/ loss of h-bond
Asp94α	-22.4	← Ⓑ Strong repulsion in oxy form
Val96α	5.5	
• Asn97α	3.3	← Ⓔ inconsistent w/ std. expla