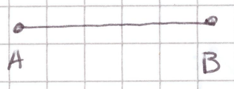
L6 Free energy calculations

1) Important: they are the driving forces of molecular processes (Dill. MDF Stat. Therm. in Chemistry and Biodogy)

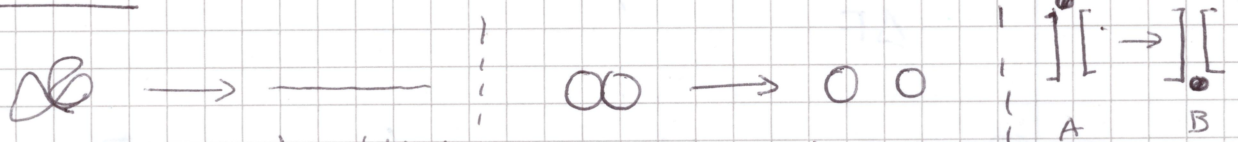
2) Process Transition definition



$\Delta F \rightarrow$ Free energy associated to the transition

$W \rightarrow$ Work done

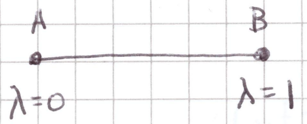
Examples



A) Folded B) Unfolded | A) Protein Complex B) Complex dissociation | ion permeation

3) How to calculate ΔF?

Let's define a reaction coordinate λ between A and B:



Hamiltonian: $H(x, P; \lambda)$

$$H(x, P; \lambda = 0) = H_A$$

$$H(x, P; \lambda = 1) = H_B$$

4) $F = -k_B T \ln Z$

$Z \rightarrow$ Partition function

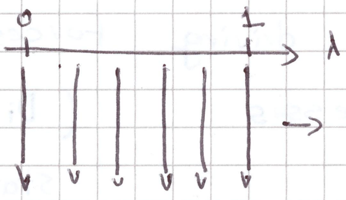
$$Z = C \iint e^{-\beta H} \, dx \, dP$$

One can demostrate that

$$\frac{\partial F}{\partial \lambda} = \left\langle \frac{\partial H}{\partial \lambda} \right\rangle \Rightarrow \Delta F = F_B - F_A = \int_{\lambda=0}^{\lambda=1} \left\langle \frac{\partial H}{\partial \lambda} \right\rangle d\lambda$$

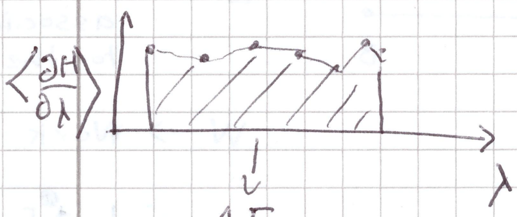
$\rightarrow$ Ensemble average

How to do it in sims:



$\rightarrow$ Simulations at different λ values.

$$\left\langle \frac{\partial H}{\partial \lambda} \right\rangle \Big|_{\lambda=0} \quad \cdots \quad \left\langle \frac{\partial H}{\partial \lambda} \right\rangle \Big|_{\lambda=1}$$



⑤ Non-equilibrium

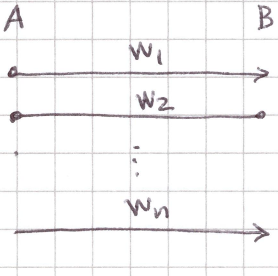
(Chap 5. Free-energy Calculations. Ed. Springer)

- From eq: only inequality:

$$W \geq \Delta F$$

- Jarzynski (Equality):

$$\left\langle e^{-\beta W} \right\rangle = e^{-\beta \Delta F}$$



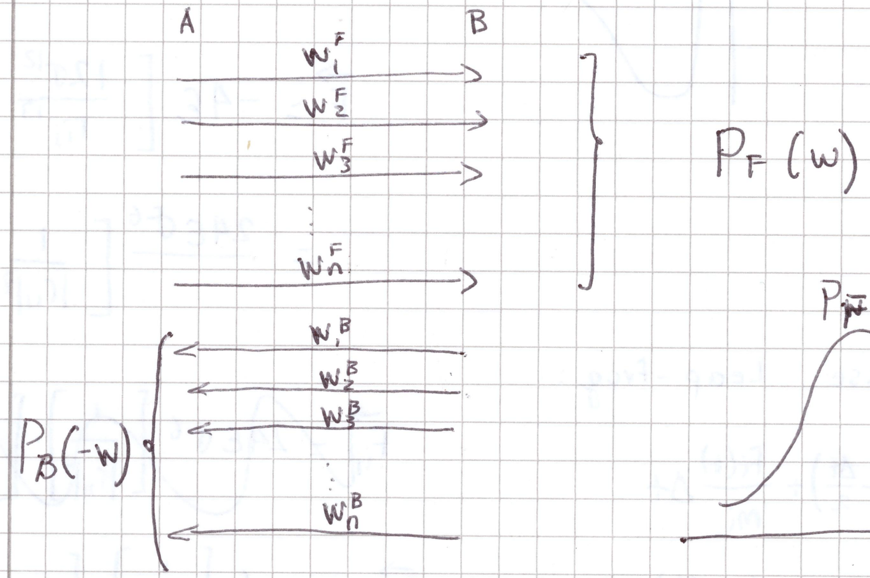
$$e^{-\beta W_1}$$
$$e^{-\beta W_2}$$
$$\vdots$$
$$e^{-\beta W_n}$$

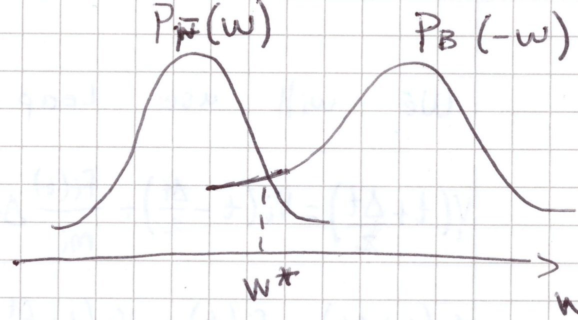
$$\left\langle e^{-\beta W} \right\rangle \xrightarrow{-\frac{1}{\beta}\ln} \Delta F$$

Not practical because only small work values contribute.

- Crooks (Consider Forward and Backwards):

$$\frac{P_F(W)}{P_B(-W)} = e^{\beta(W-\Delta F)}$$





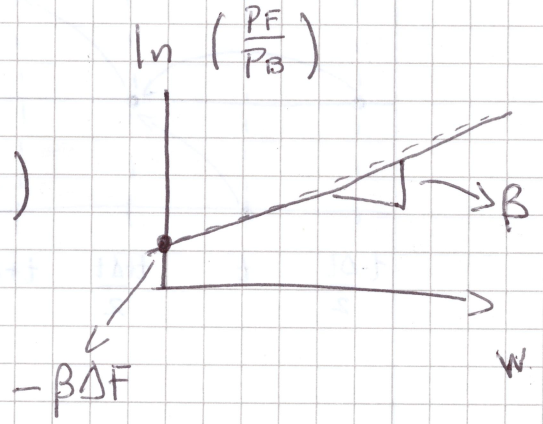
<u>way 1:</u>

For ω^* $P_F(\omega^*) = P_B(-\omega^*) \Rightarrow \omega^* = \Delta F$

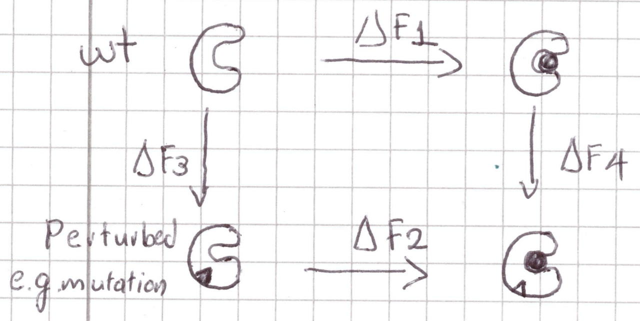
<u>way 2:</u>

take logarithm:

$$\ln\left(\frac{P_F}{P_B}\right) = \beta\,(W-\Delta F)$$



(6) Thermodynamic cycles:



ΔF_1 && ΔF_2 are often difficult to calculate directly.

<u>Alternative:</u> Calculate ΔF_3 & ΔF_4 minimal changes

$$\Delta F_1 + \Delta F_4 = \Delta F_3 + \Delta F_2$$

$$\Delta\Delta F = \underbrace{\Delta F_3 - \Delta F_4}_{\text{Calculated}} = \Delta F_1 - \Delta F_2$$

$\Delta\Delta F > 0 \Rightarrow \Delta F_1 > \Delta F_2$ Perturbed route more Favourable | $\Delta\Delta F < 0 \Rightarrow \Delta F_1 < \Delta F_2$ wt route more Favourable