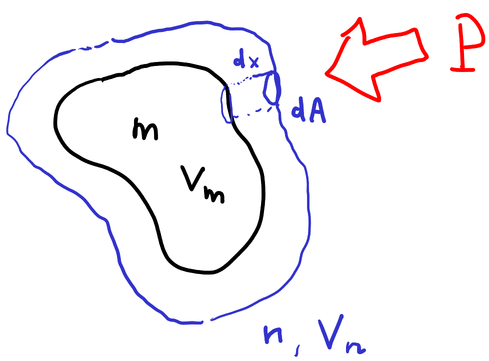
$$\frac{\Omega_{nm}}{\Omega_{mn}} = e^{-\beta\left(\underbrace{E_n - E_m}_{\substack{Q_{nm} \\ \text{heat provided} \\ \text{by env.}}} - \underbrace{W_{nm}}_{\substack{\text{work by env.} \\ \text{on sys.}}}\right)}$$

Go into details of typical W_{nm} for biological systems:

- work against pressure
- "chemical" work $\Rightarrow$ chemical potentials

Pressure: biomolecule $m \rightleftarrows n$

volume V_m volume V_n



$$\begin{array}{c}\text{Work}\\ \text{done}\\ \text{by}\\ \text{sys on}\\ \text{env.}\end{array} = \int_{\text{area}} \overbrace{P\,dA}^{\text{force}}\ \overbrace{dx}^{\text{distance}} \quad \text{with } \underbrace{dA\,dx}_{dV \text{ volume element}}$$

$$= P(V_n - V_m)$$

$$\underset{\text{by env. on sys}}{W_{nm}} = -P(V_n - V_m)$$

$$= A_n - A_m \quad \text{conservative work}$$

where $A_n \equiv -PV_n$

$$\Rightarrow \frac{\Omega_{nm}}{\Omega_{mn}} = e^{-\beta(E_n - E_m + PV_n - PV_m)}$$

$$\equiv e^{-\beta (H_n - H_m)}$$

where

$$H_n \equiv E_n + P V_n$$

new state variable

$\equiv$ enthalpy of state n

$\Rightarrow$ ESS where E_n are replaced by H_n:

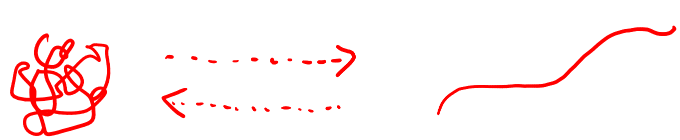
$$p_n^s = \frac{e^{-\beta H_n}}{Z} \qquad Z = \sum_n e^{-\beta H_n}$$

in general: $$\frac{\Omega_{nm}}{\Omega_{mn}} = e^{-\beta (H_n - H_m - W_{nm})}$$

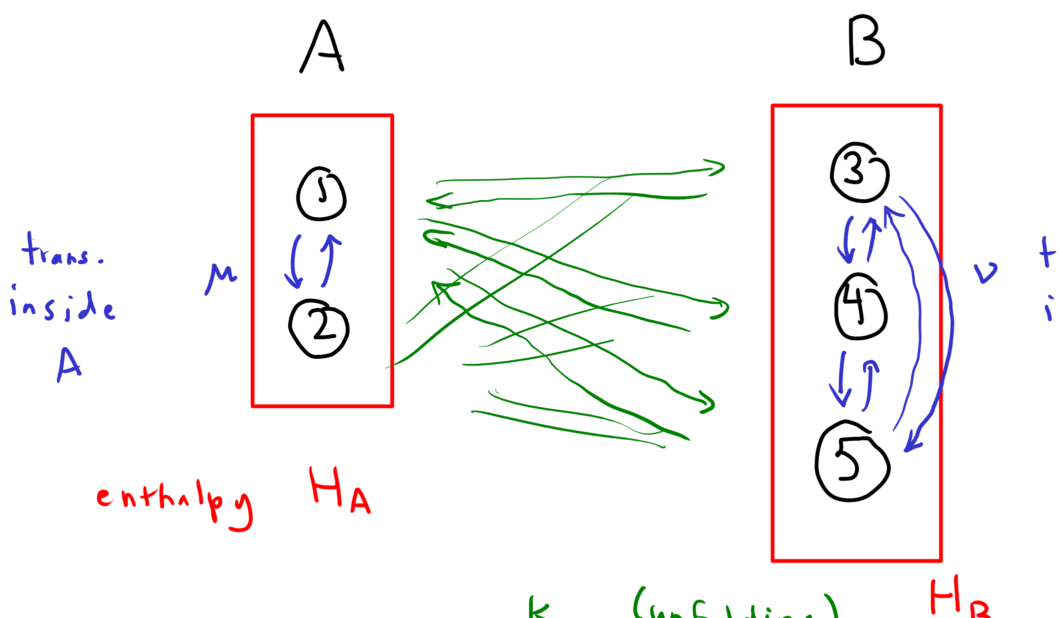
non-pressure work terms

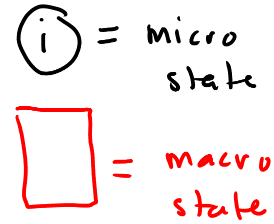
Most biological "states" are coarse-grained descriptions ("macrostates") corresponding to many possible "microstates".

simple protein model: folded state unfolded state



macrostate A B





$H_1 = H_2 = H_A$

$H_3 = H_4 = H_5 = H_B$

any arrow b/t boxes
$$\begin{cases} A \xrightarrow{k_u} B & \text{(unfolding)} \\ B \xrightarrow{k_f} A & \text{(folding)} \end{cases}$$

$\sigma_A = \#$ micro states in A $= 2$

$\sigma_B = 3$

Goal: create a coarse-grained (2-state) master equ. for A, B given original system (5 states) + rates

map onto:
$$A \underset{\Omega_{BA}}{\overset{\Omega_{AB}}{\leftrightarrows}} B$$

can we find Ω_{AB} + Ω_{BA} such that physics is $\approx$ same as original

often this mapping works best when we have a "separation of timescales"

$\mu, \nu \gg k_u, k_f$ int. rates $\gg$ ext. rates write down master equ. for orig. model:

$$\frac{dp_1}{dt} = -3k_u p_1 - \mu p_1 + k_f(p_3 + p_4 + p_5) + \mu p_2$$

$$\frac{dp_2}{dt} = -3k_u p_2 - \mu p_2 + k_f(p_3 + p_4 + p_5) + \mu p_1$$

... equ's for p_3, p_4, p_5, etc.

coarse-grained prob.: $p_A = p_1 + p_2$

$p_B = p_3 + p_4 + p_5$

$$\Rightarrow \quad \frac{d}{dt}(p_1 + p_2) = -3k_u(p_1 + p_2) + 2k_f(p_3 + p_4 + p_5)$$

$$\frac{d}{dt} p_A = -3k_u p_A + 2k_f p_B$$

similar steps

$$\frac{d}{dt} p_B = 3k_u p_A - 2k_f p_B$$

$\Omega_{AB} = 2k_f = \sigma_A k_f$ in general

$$A \underset{\Omega_{BA}}{\overset{\Omega_{AB}}{\rightleftarrows}} B$$

$\Omega_{BA} = 3k_u = \sigma_B k_u$ in general

$\Omega_{mn} = \sigma_m k_{mn}$ ← microstate to microstate rate

generalize: macrostate

$$n \underset{\Omega_{nm}}{\overset{\Omega_{mn}}{\rightleftarrows}} m$$

$\Omega_{nm} = \sigma_n k_{nm}$