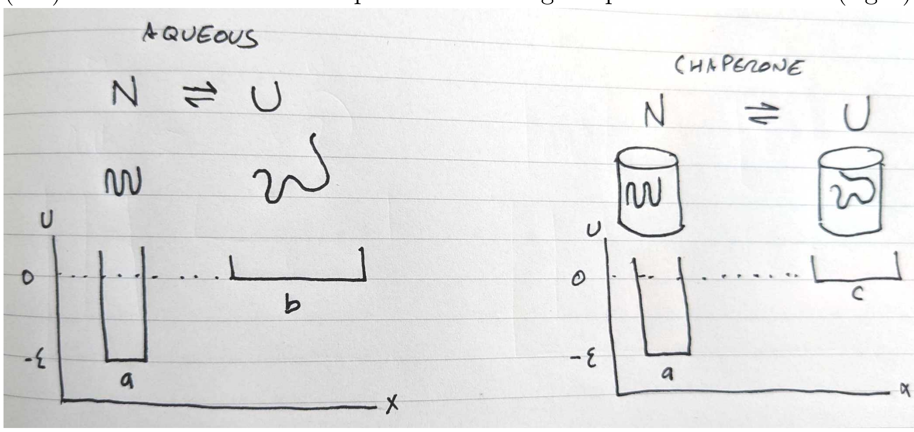
# Stat Mech Exam Question – Nov 2019

Consider a simple model of two-state protein folding either in aqueous solution (left) or inside the confined space of a folding chaperone like GroEL (right):




Presume the protein is in equilibrium between the native state (N) and the unfolded state (U). We'll make a simple one-dimensional model to illustrate the effect of confinement by a molecular chaperone on folding equilibria.

In both cases, the native state (N) is compact—let's assume that it has a one-dimensional width of $a$, where every microstate has energy $-\epsilon$.

For simplicity, we'll assume that every microstate in the unfolded state has energy 0. In aqueous solution, we'll presume the width of the unfolded state is $b$; for real proteins, the radius of gyration—a measure of the compactness of the protein—of the unfolded state is $b \sim 2.5a$. Inside the chaperone, however, the unfolded protein cannot expand quite so much—let's presume that the unfolded state in the chaperone has $c \sim 1.5a$ simply because of the confinement effect.

*(a)* What is the free energy of unfolding $\Delta F^{\mathrm{aq}}_{N\to U} = F^{\mathrm{aq}}_U - F^{\mathrm{aq}}_N$ in aqueous solution?

*(b)* What is the free energy of unfolding $\Delta F^{\mathrm{ch}}_{N\to U} = F^{\mathrm{ch\,ch}}_U - F_N$ in the confinement of the chaperone?

*(c)* What is the native state stabilization free energy $\Delta\Delta F = F^{\mathrm{ch}}_{N\to U} - F^{\mathrm{aq}}_{N\to U}$ provided by confinement within the chaperone at 300 K?

*(d)* If only 50% of the protein is folded in aqueous solution at equilibrium, how much does this shift the equilibrium in the presence of confinement within the chaperone in terms of percent folded?

# Stat Mech Exam Question – Nov 2019 – Solution

*(a)*

$$
\begin{aligned}
\Delta F^{\text{aq}}_{N\to U} &= F^{\text{aq}}_U - F^{\text{aq}}_N && (1)\\
&= [0 - k_BT\ln b] - [-\epsilon - k_BT\ln a] && (2)\\
&= \epsilon - k_BT\ln\frac{b}{a} && (3)\\
&= \epsilon - k_BT\ln\frac{2.5a}{a} && (4)\\
&= \epsilon - k_BT\ln 2.5 && (5)\\
& && (6)
\end{aligned}
$$

*(b)*

$$
\begin{aligned}
\Delta F^{\text{aq}}_{N\to U} &= F^{\text{aq}}_U - F^{\text{aq}}_N && (7)\\
&= [0 - k_BT\ln c] - [-\epsilon - k_BT\ln a] && (8)\\
&= \epsilon - k_BT\ln\frac{c}{a} && (9)\\
&= \epsilon - k_BT\ln\frac{1.5a}{a} && (10)\\
&= \epsilon - k_BT\ln 1.5 && (11)\\
& && (12)
\end{aligned}
$$

*(c)*

$$
\begin{aligned}
\Delta\Delta F &= F^{\text{ch}}_{N\to U} - F^{\text{aq}}_{N\to U} && (13)\\
&= [\epsilon - k_BT\ln 1.5] - [\epsilon - k_BT\ln 2.5] && (14)\\
&= k_BT\ln\frac{2.5}{1.5} && (15)\\
&\sim (0.6\ \text{kcal/mol})\ln 1.7 && (16)\\
&\sim 0.3\ \text{kcal/mol} && (17)
\end{aligned}
$$

*(d)* 50% unfolded in aqueous solution implies $\Delta F^{\text{aq}}_{N\to U} = 0$ kcal/mol, so $\Delta F^{\text{ch}}_{N\to U} =$ 0.3 kcal/mol. To compute the percent folded in the chaperone, we know $f_U/f_N = e^{-\Delta F^{\text{ch}}_{N\to U}/k_BT}$, so $f_U/f_N = e^{-0.3/0.6} = 0.6$, where $f_N + f_U = 1$. That gives us

$$
\begin{aligned}
(1-f_N)/f_N &= 0.6 && (18)\\
1 - f_N &= 0.6f_N && (19)\\
f_N &= 1/1.6 = 0.625 && (20)
\end{aligned}
$$

so the increase is from 50% to 62.5%, which is an increase of 12.5%.