PHYS3511-Biological Physics

Fall 2018, Assignment #7 Due Thursday November 22, 2018

Read Chapter 7: section 7.1 and 7.2 page 281 to 303. The information on these sections may be used in multiple-choice questions in **quiz 2** and the **final exam**.

Exercise 1) (10 points) Do problem 7.3 of Chapter 7

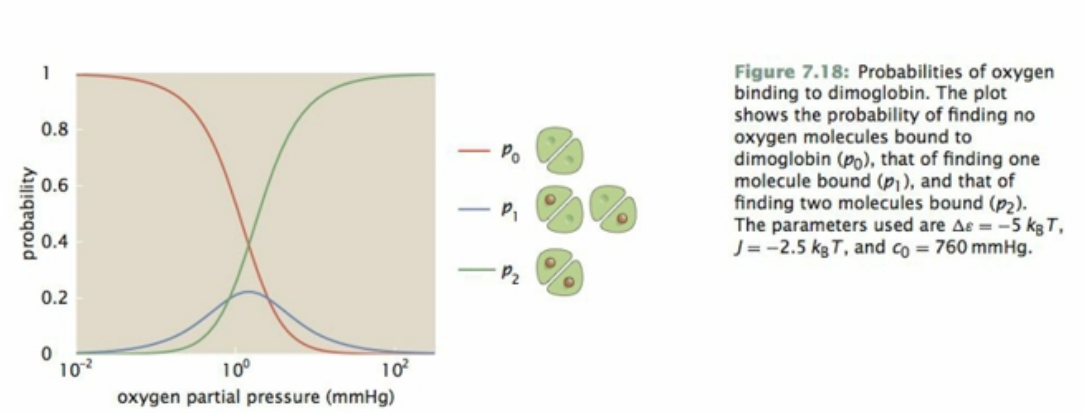
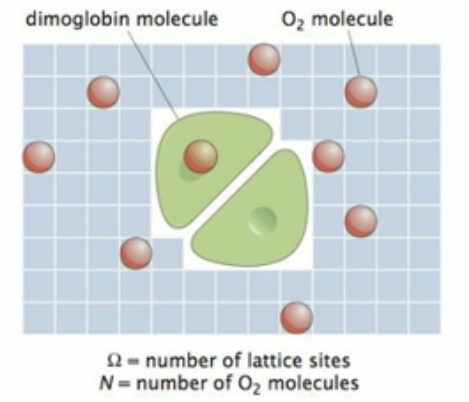


Figure 7.18: Probabilities of oxygen binding to dimoglobin. The plot shows the probability of finding no oxygen molecules bound to dimoglobin (p_0), that of finding one molecule bound (p_1), and that of finding two molecules bound (p_2). The parameters used are $\Delta\varepsilon = -5\ k_B T$, $J = -2.5\ k_B T$, and $c_0 = 760$ mmHg.

Toy Model of a Dimeric Hemoglobin (Dimoglobin) with oxygens on lattice



Define N as the number of O_2 molecule and Ω the number of lattice sites. If an O_2 molecule occupies a lattice site then it has the energy ε_{sol} and if it is bounded to one of the **two dimoglobin sites** then its **energy** is ε. If two oxygens are bounded then there is an energy of J. We have the following energy and multiplicity.

No bound oxygen: $\sigma_1 = \sigma_2 = 0$; N oxygens on lattice, **energy** $E(\sigma_1, \sigma_2) = E(0,0) = N\varepsilon_{sol}$; **multiplicity** of microstates with the same energy $\frac{\Omega!}{N!(\Omega-N)!}$.

One bound oxygen: $\sigma_1 = 1, \sigma_2 = 0$ and $\sigma_1 = 0, \sigma_2 = 1$; $N-1$ oxygens on lattice; **energy** $E(1,0) = E(0,1) = (N-1)\varepsilon_{sol} + \varepsilon$; **multiplicity** of microstates with the same energy $\frac{\Omega!}{(N-1)!(\Omega-N+1)!}$.

Two bound oxygens: $\sigma_1 = 1, \sigma_2 = 1$; $N-2$ oxygens on lattice; **energy** $E(1,1) = E(1,1) = (N-2)\varepsilon_{sol} + 2\varepsilon + J$; **multiplicity** of microstates with the same energy $\frac{\Omega!}{(N-2)!(\Omega-N+2)!}$.

$$Z = \frac{\Omega!}{N!\,(\Omega-N)!} exp(-\beta N\varepsilon_{sol}) + 2 \times \frac{\Omega!}{(N-1)!\,(\Omega-N+1)!}\ exp(-\beta((N-1)\varepsilon_{sol} + \varepsilon) + \frac{\Omega!}{(N-2)!\,(\Omega-N+2)!} exp(-\beta[(N-2)\varepsilon_{sol} + 2\varepsilon + J])$$

Now we assume that both Ω and N are **very large**, and that $\Omega \gg N$ (i.e. dilute concentration of oxygens), we the employed the better version of Stirling's approximation (see equation 6.15) to show

$$\frac{\Omega!}{(\Omega - N)!} \approx \Omega^N$$

This gives

$$Z = \frac{\Omega^N}{N!} exp(-\beta N \varepsilon_{sol}) + 2 \times \frac{\Omega^{N-1}}{(N-1)!}\, exp\left(-\beta\big((N-1)\varepsilon_{sol} + \varepsilon\big)\right) + \frac{\Omega^{N-2}}{(N-2)!} exp(-\beta[(N-2)\varepsilon_{sol} + 2\varepsilon + J])$$

Using $\langle N \rangle = \sum_{\sigma_1,\sigma_2=0,1} (\sigma_1 + \sigma_2) P(\sigma_1, \sigma_2)$

$$\langle N \rangle = \frac{2\frac{\Omega^{N-1}}{(N-1)!}\, exp\left(-\beta\big((N-1)\varepsilon_{sol} + \varepsilon\big)\right) + 2\frac{\Omega^{N-2}}{(N-2)!} exp(-\beta[(N-2)\varepsilon_{sol} + 2\varepsilon + J])}{Z}$$

or

$$\langle N \rangle = \frac{2\frac{\Omega^{N-1}}{(N-1)!}\, exp\left(-\beta\big((N-1)\varepsilon_{sol} + \varepsilon\big)\right) + 2\frac{\Omega^{N-2}}{(N-2)!} exp(-\beta[(N-2)\varepsilon_{sol} + 2\varepsilon + J])}{\frac{\Omega^N}{N!} exp(-\beta N \varepsilon_{sol}) + 2 \times \frac{\Omega^{N-1}}{(N-1)!}\, exp\left(-\beta\big((N-1)\varepsilon_{sol} + \varepsilon\big)\right) + \frac{\Omega^{N-2}}{(N-2)!} exp(-\beta[(N-2)\varepsilon_{sol} + 2\varepsilon + J])}$$

Now we divide **numerator** and **denominator** by $\frac{\Omega^N}{N!} exp(-\beta N \varepsilon_{sol})$ to obtain

$$\langle N \rangle = \frac{2\frac{\mathrm{N}}{\Omega}\, exp\big(-\beta(\varepsilon - \varepsilon_{sol})\big) + 2\frac{\mathrm{N}(N-1)}{\Omega^2}\, exp\big(-\beta(2(\varepsilon - \varepsilon_{sol}) + J)\big)}{1 + 2 \times \frac{\mathrm{N}}{\Omega}\, exp\big(-\beta(\varepsilon - \varepsilon_{sol})\big) + 2 \times \frac{\mathrm{N}(N-1)}{\Omega^2}\, exp\big(-\beta(2(\varepsilon - \varepsilon_{sol}) + J)\big)}$$

Assuming that the number of O_2 is large, $\mathrm{N}(N-1) \sim N^2$, we obtain

$$\langle N \rangle = \frac{2\frac{N}{\Omega} exp(-\beta\Delta\varepsilon) + 2\frac{N^2}{\Omega^2} exp\big(-\beta(2\Delta\varepsilon + J)\big)}{1 + 2\frac{N}{\Omega} exp(-\beta\Delta\varepsilon) + \frac{N^2}{\Omega^2} exp\big(-\beta(2\Delta\varepsilon + J)\big)},$$

with $\Delta\varepsilon = \varepsilon - \varepsilon_{sol}$. Writing

$$\frac{N}{\Omega} = \frac{\left(\frac{N}{\Omega V_{box}}\right)}{\left(\frac{1}{V_{box}}\right)} = \frac{c}{c_0},$$

where $c = \frac{N}{\Omega V_{box}}$, since ΩV_{box} total volume of the system, and $c_0 = \frac{1}{V_{box}}$ is the reference concentration, i.e. the concentration for **one** molecule (such as O_2) in a volume V_{box}. As discussed in class (and in the textbook) V_{box} is the volume occupied by one lattice (the blue square in the figure on the previous page). The value is arbitrary, but the textbook chooses $V_{box} = 1nm^3$. Substituting $\frac{N}{\Omega} = \frac{c}{c_0}$ gives

$$\langle N\rangle = \frac{2\left(\frac{c}{c_0}\right)exp(-\beta\Delta\varepsilon) + 2\left(\frac{c}{c_0}\right)^2 exp\big(-\beta(2\Delta\varepsilon + J)\big)}{1 + 2\left(\frac{c}{c_0}\right)exp(-\beta\Delta\varepsilon) + \left(\frac{c}{c_0}\right)^2 exp\big(-\beta(2\Delta\varepsilon + J)\big)},$$

which is identical to equation 7.32.
This completes part A of the question.
Part B)
From the previous part A

$$Z = \frac{\Omega!}{N!\,(\Omega - N)!}exp(-\beta N\varepsilon_{sol}) + 2 \times \frac{\Omega!}{(N-1)!\,(\Omega - N + 1)!}\,exp(-\beta((N-1)\varepsilon_{sol} + \varepsilon) + \frac{\Omega!}{(N-2)!\,(\Omega - N + 2)!}exp(-\beta[(N-2)\varepsilon_{sol} + 2\varepsilon + J])$$

it is clear that the first, second and third terms are associated with the probability that **no** O_2, **one** O_2, and **two** O_2, respectively, are bounced to the dimoglobin. We can infer from this:

$$P_0 = \frac{1}{1 + 2\left(\frac{c}{c_0}\right)exp(-\beta\Delta\varepsilon) + \left(\frac{c}{c_0}\right)^2 exp\big(-\beta(2\Delta\varepsilon + J)\big)}$$

$$P_1 = \frac{2\left(\frac{c}{c_0}\right)exp(-\beta\Delta\varepsilon)}{1 + 2\left(\frac{c}{c_0}\right)exp(-\beta\Delta\varepsilon) + \left(\frac{c}{c_0}\right)^2 exp\big(-\beta(2\Delta\varepsilon + J)\big)}$$

$$P_2 = \frac{\left(\frac{c}{c_0}\right)^2 exp\big(-\beta(2\Delta\varepsilon + J)\big)}{1 + 2\left(\frac{c}{c_0}\right)exp(-\beta\Delta\varepsilon) + \left(\frac{c}{c_0}\right)^2 exp\big(-\beta(2\Delta\varepsilon + J)\big)}.$$

From the figure caption 7.18

$$\frac{\Delta\varepsilon}{k_BT} = -5; \frac{J}{k_BT} = -2.5,$$

which gives

$$exp(-\beta\Delta\varepsilon) = 148.4; exp(-\beta 2\Delta\varepsilon) = 2.2 \times 10^4;\ exp\big(-\beta(2\Delta\varepsilon + J)\big) = 268337;$$

Now we note that the partial pressure of oxygen can be given by the ideal gas approximation

$$P_{oxygen} = ck_BT; P_{reference} = c_0k_BT; \frac{c}{c_0} = \frac{P_{oxygen}}{P_{reference}}.$$

On the figure caption it is stated that $P_{reference} = c_0 = 760mmHg$. Let's pick a ubiquitous point on Figure 7.18 $P_{oxygen} = c = 10^0 mmHg = 1mmHg$,

$$\frac{c}{c_0} = \frac{1}{760}; \left(\frac{c}{c_0}\right)^2 = \left(\frac{1}{760}\right)^2$$

which gives

$$P_0 = \frac{1}{1 + 2\left(\frac{1}{760}\right)148.4 + \left(\frac{1}{760}\right)^2 268337} = \frac{1}{1 + 0.39 + .464} = \frac{1}{1.854} = 0.54,$$

$$P_1 = \frac{2\left(\frac{1}{760}\right)148.4}{1 + 2\left(\frac{1}{760}\right)148.4 + \left(\frac{1}{760}\right)^2 268337} = \frac{0.39}{1.854} = 0.21,$$

$$P_2 = \frac{\left(\frac{1}{760}\right)^2 268337}{1 + 2\left(\frac{1}{760}\right)148.4 + \left(\frac{1}{760}\right)^2 268337} = \frac{0.464}{1.854} = 0.25.$$

If you look at Figure 7.18 on the first page we can see that thes are the correct values.

Exercise 2) (**10 points**) Chapter 7, Problem 7.5

A) we generalized equation 6.120 for two ligands CO and O_2 to give the probability of bound O_2,

$$P_{O_2} = \frac{\left(\frac{[O_2]}{K_{O_2}}\right)^{n_{O_2}}}{1 + \left(\frac{[O_2]}{K_{O_2}}\right)^{n_{O_2}} + \left(\frac{[CO]}{K_{CO}}\right)^{n_{CO}}},$$

$[O_2] = 0.21atm^{-1}\frac{760mmHg}{1tam} = 159.6mmHg$; $K_{O_2} = 26mmHG$; $[CO] = 2mmHg$; $K_{CO} = \frac{1}{240}K_{O_2} = 0.108mmHG$; $n_{O_2} = 3.0$; $n_{CO} = 1.4$.This gives

$$P_{O_2} = \frac{\left(\frac{159.6mmHg}{26mmHG}\right)^{3.0}}{1 + \left(\frac{159.6mmHg}{26mmHG}\right)^{3.0} + \left(\frac{2mmHg}{0.108mmHG}\right)^{1.4}} = \frac{231.3}{1 + 231.3 + 59.5} = 0.79$$

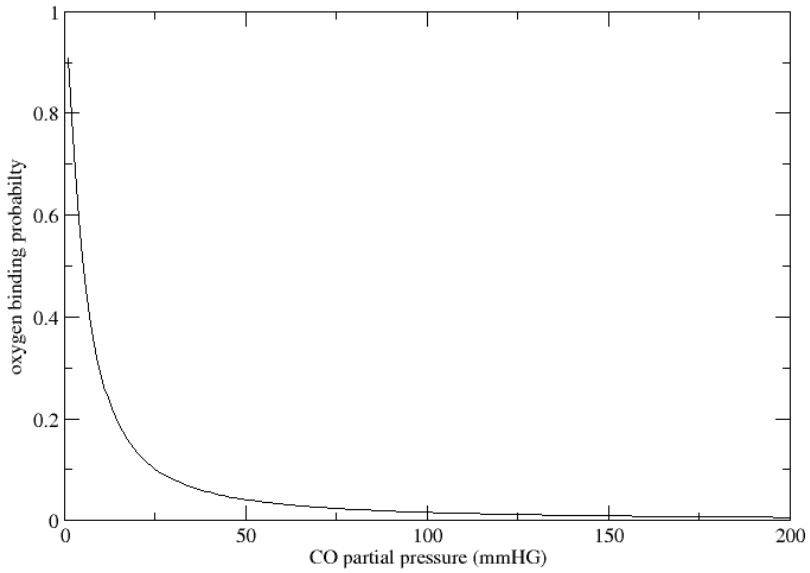
$$P_{CO} = \frac{\left(\frac{[CO]}{K_{CO}}\right)^{n_{CO}}}{1 + \left(\frac{[O_2]}{K_{O_2}}\right)^{n_{O_2}} + \left(\frac{[CO]}{K_{CO}}\right)^{n_{CO}}},$$

$$P_{CO} = \frac{\left(\frac{2mmHg}{0.108mmHG}\right)^{1.4}}{1 + \left(\frac{159.6mmHg}{26mmHG}\right)^{3.0} + \left(\frac{2mmHg}{0.108mmHG}\right)^{1.4}} = 0.21.$$

B) Write

$$P_{O_2} = \frac{\left(\frac{159.6mmHg}{26mmHG}\right)^{3.0}}{1 + \left(\frac{159.6mmHg}{26mmHG}\right)^{3.0} + \left(\frac{CO\ partical\ Pressure}{0.108mmHG}\right)^{1.4}}$$

Plot is shown below



C) equating the probability

$$P_{O_2} = \frac{\left(\frac{[O_2]}{K_{O_2}}\right)^{n_{O_2}}}{1+\left(\frac{[O_2]}{K_{O_2}}\right)^{n_{O_2}}+\left(\frac{[CO]}{K_{CO}}\right)^{n_{CO}}} = P_{CO} = \frac{\left(\frac{[CO]}{K_{CO}}\right)^{n_{CO}}}{1+\left(\frac{[O_2]}{K_{O_2}}\right)^{n_{O_2}}+\left(\frac{[CO]}{K_{CO}}\right)^{n_{CO}}}$$

After canceling the denominator

$$\left(\frac{[O_2]}{K_{O_2}}\right)^{n_{O_2}} = \left(\frac{[CO]}{K_{O_2}}\right)^{n_{CO}} \rightarrow \left(\frac{[O_2]}{K_{O_2}}\right)^{n_{O_2}}\left(\frac{K_{CO}}{[CO]}\right)^{n_{co}} = 1$$

$$[CO] = K_{CO}\left(\frac{[O_2]}{K_{O_2}}\right)^{n_{O_2/n_{CO}}} = 0.108mmHg\left(\frac{159.6mmHg}{26mmHG}\right)^{3.0/1.4} = 5.3mmHg$$

Exercise 3) (**10 points**) Chapter 7, Problem 7.6

Preamble: partition function $Z = \sum_\varepsilon g exp(-\beta\varepsilon)(\varepsilon)exp(-\beta\varepsilon)$, where the summation is over all microstates, and ε is the energy of a group of microstates with the same energy, and $g(\varepsilon)$ is the multiplicity or the number of microstates that has the energy ε. The probability that a microstate with energy ε is occupied is simply $P(\varepsilon) = \frac{g(\varepsilon)exp(-\beta\varepsilon)}{Z}$.

A) Compact microstate: energy zero, multiplicity g(0) = 1; open state energy ε, multiplicity $g(\varepsilon) = 3$.

$$Z = 1 + 3exp(-\beta\varepsilon);$$

open (o) conformation probability is

$$P_o = \frac{g(\varepsilon)exp(-\beta\varepsilon)}{Z} = \frac{3exp(-\beta\varepsilon)}{1+3exp(-\beta\varepsilon)}$$

closed conformation probability is

$$P_c = \frac{g(0)exp(-\beta 0)}{Z} = \frac{1}{1+3exp(-\beta\varepsilon)}$$

B) Large temperature $T \to \infty$ and $\beta = \frac{1}{k_B T} \to 0$ and $exp(-\beta\varepsilon) \to 1$, which gives

$$P_o = \frac{3exp(-\beta\varepsilon)}{1 + 3exp(-\beta\varepsilon)} = \frac{3}{4}; P_c = \frac{1}{1 + 3exp(-\beta\varepsilon)} = \frac{1}{4}$$

Very Low Temperature $T \to 0$ and $\beta = \frac{1}{k_B T} \to \infty$ and $exp(-\beta\varepsilon) \to 0$,

$$P_o = \frac{3exp(-\beta\varepsilon)}{1 + 3exp(-\beta\varepsilon)} = 0; P_c = \frac{1}{1 + 3exp(-\beta\varepsilon)} = 1$$

At very low temperature the protein will occupy the compact state with probability 1.

C) Average energy

$$\langle E \rangle = \sum_\varepsilon \varepsilon P(\varepsilon) = \frac{\sum_\varepsilon \varepsilon g(\varepsilon)}{Z} = \frac{0\times(0)exp(-\beta 0)+\varepsilon 3exp(-\beta\varepsilon)}{1+3exp(-\beta\varepsilon)} = \frac{3\varepsilon exp(-\beta\varepsilon)}{1+3exp(-\beta\varepsilon)}.$$

Bonus) (15 points) Just like problem 7.3 we will revisit the MWC model (page 300 to 301), but we will allow N oxygens (O_2) to occupy Ω lattice sites. Now derive the relation 7.36, but with $x = \frac{c}{c_0} exp\big(-\beta(\varepsilon_T - \varepsilon_{sol})\big)$ and $y = \frac{c}{c_0} exp\big(-\beta(\varepsilon_R - \varepsilon_{sol})\big)$, where $\varepsilon_{sol}$is the energy of the ligand (oxygen) in water, used in the ligand-receptor model in section 6.1.1. Below is the plot of the MWC model. Pick at least 2 points from each of the 3 curves to verify that the values shown in the caption is consistent.

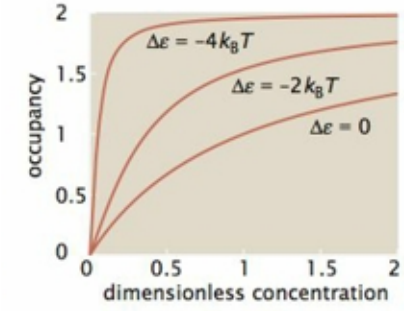


Figure 7.21: Average number of bound receptors in dimoglobin for the MWC model. The dimensionless concentration is written as $x = (c/c_0)e^{-\beta(\varepsilon_T - \mu_0)}$, where ε_T is the binding free energy of the ligand in the tense state. $\Delta\varepsilon$ is the difference between the binding energy in the relaxed and tense states. For the plots shown here, $\varepsilon = 2\,k_B T$.

• 7.3 Dimoglobin revisited

(a) Use the canonical distribution (as in Section 6.1.1 on p. 241) to redo the problem of dimoglobin binding. For simplicity, imagine a box with N O_2 molecules that can be distributed among Ω sites. This simple lattice model of the solution is intended to account for the configurational entropy available to the O_2 molecules when they are in solution. This disposition of the system is shown in Figure 7.29. Use the energy given in Equation 7.29 when constructing the partition function.

(b) Figure 7.18 shows the probabilities of the various states available to dimoglobin in its interactions with its oxygen binding partners. Write expressions for the probabilities p_0, p_1, and p_2 corresponding to occupancy 0, 1, and 2, respectively. Using the parameters shown in the caption to Figure 7.18, reproduce the plot.

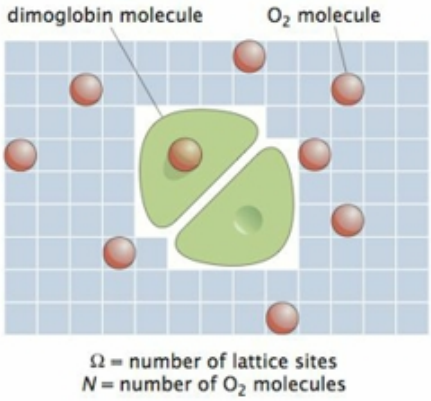


Figure 7.29: Schematic of the binding assay of interest in which the oxygen molecules can be either bound to dimoglobin or in solution.

• 7.4 State probabilities in the MWC model

Plot p_0, p_1, and p_2, the probabilities of different states of occupancy for both the T and R states for the MWC model of dimoglobin. Use the same parameters to generate your plot that were used to generate Figure 7.21.

• 7.5 Carbon monoxide and hemoglobin

Carbon monoxide is a deadly gas that binds hemoglobin roughly 240 times as tightly as oxygen does (this means that CO has 1/240 the dissociation constant of O_2, or $240K_{CO} = K_{O_2}$, where $K_{O_2} = 26$ mmHg).

(a) When both CO and O_2 are present, use the Hill equation introduced in Section 6.4.3 to calculate the probability that hemoglobin will be saturated with oxygen. Similarly, compute the probability that hemoglobin will be saturated with CO. Calculate the partial pressure of oxygen using the fact that atmospheric oxygen constitutes roughly 21% of air and assume a partial pressure of CO of 2 mmHg. Hemoglobin binding to carbon monoxide has a Hill coefficient of 1.4 and hemoglobin binding to oxygen has a Hill coefficient of 3.0.

(b) Plot the probability of O_2 binding to hemoglobin as a function of the partial pressure of CO assuming the oxygen partial pressure remains constant.

(c) Show that CO and O_2 will have an equal probability of binding when the condition

$$\left(\frac{[O_2]}{K_{O_2}}\right)^{n_{O_2}} \left(\frac{K_{CO}}{[CO]}\right)^{n_{CO}} = 1$$

is satisfied and work out the partial pressure of CO at which this occurs.

• 7.6 Toy model of protein folding

A four-residue protein can take on the four different conformations shown in Figure 7.30. Three conformations are open and have energy ε ($\varepsilon > 0$) and one is compact, and has energy zero.

(a) At temperature T, what is the probability, p_o, of finding the molecule in an open conformation? What is the probability, p_c, that it is compact?

(b) What happens to the probability p_c, calculated in (a), in the limit of very large and very low temperatures.

(c) What is the average energy of the molecule at temperature T?

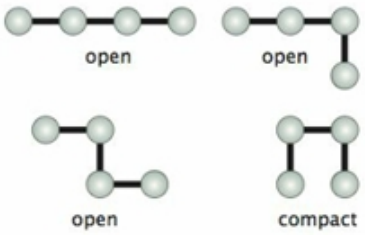


Figure 7.30: Toy model of protein folding showing four different conformations. (Adapted from K. Dill and S. Bromberg, Molecular Driving Forces, 2nd ed. Garland Science, 2011.)

• 7.7 Chemical potentials and channel open probabilities

An alternative way to think of the probability of gating of membrane-bound channels is to think of the membrane as consisting of two species of channel, closed and open, at concentrations c_{closed} and c_{open}, respectively. These two species are subject to constant interconversion characterized by an equilibrium in which their respective chemical potentials are equal. By setting the chemical potentials for these two species equal, work out an expression for the open probability.

• 7.8 Energy landscapes in the two-state model

Draw an energy landscape such as shown in Figure 7.7 for the voltage-gated sodium channel presented in Figure 7.2. In particular, show how the landscape changes as a function of the applied voltages shown in Figure 7.2(C). Explain your reasoning carefully.