Assignment 2
Biophys 4322/5322

Tyler Shendruk

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1 Problem 1) Phillips 5.1

1.1 Part a)

How many molecules of glucose must be taken up to provide the carbon skeleton for serine? Draw the biochemical pathway starting with glucose and ending in serine. Label the energy requiring and energy generating steps. How many molecules of ATP are consumed and created along the way? How many equivalents of NADH and NADPH are consumed or created? Assuming that each NADH and NADPH is equivalent to 2 ATP, what is the net energy cost to synthesize one molecule of serine in units of ATP and units of k_BT?

Glucose has 6C but serine has only 3C. So only 1/2C is need for 1 serine. For this reason, let's follow the production of two serines and then when we are finished counting, we will divide our answer in half.

$$
\begin{array}{rll}
\text{glucolysis} & \left\{\begin{array}{l}
\text{1 glucose}\\
\downarrow\\
\text{1 glucose-6-phosphate}\\
\downarrow\\
\text{1 fructose-1,6-biphosphate}\\
\downarrow\\
\text{2 1-3-diphosphate glycerate}
\end{array}\right. &
\begin{array}{l}
\\
-1\text{ ATP}\\
\\
-1\text{ ATP}\\
\\
+2\text{ NADH}\\
\\
\end{array}\\
& \downarrow & +2\text{ ATP}\\
\text{serine synthesis} & \left\{\begin{array}{l}
\text{2 3-phosphoglycerate}\\
\downarrow\\
\text{2 3-phosph-hydroxypyruvate}\\
\downarrow\\
\text{2 glutomate}
\end{array}\right. &
\begin{array}{l}
\\
+2\text{ NADH}\\
\\
\\
\\
\end{array}\\
& \swarrow\searrow \qquad\qquad \nwarrow & -2\text{ NADPH}\\
& \text{2 serine} \qquad \text{2 2-ketogluterate} &
\end{array}
$$

So then our net count for creating two serines is $\begin{array}{l|c} \text{Net ATP} & 0 \\ \text{Net NADH} & +4 \\ \text{Net NADPH} & \text{-2} \end{array}$ which means that our net for a single serine is $\begin{array}{l|c} \text{Net ATP} & 0 \\ \text{Net NADH} & +2 \\ \text{Net NADPH} & \text{-1} \end{array}$

This is equivalent to +2 ATP or $\approx 40 k_\mathrm{B} T$.

2 Problem 2) Phillips 5.3

2.1 Part a)

Based on a typical bond energy of $-\epsilon = 150 k_\mathrm{B} T = 150 \times 4.1 \times 10^{-21} J = 6 \times 10^{-19} J$ and a typical bond length of $r_m = 1.5$Å$= 1.5 \times 10^{-10} m$, use dimensional analysis to estimate the frequency of vibration of covalent bonds. By unit analysis

$$\epsilon = m \left(\frac{r_m}{\tau} \right)^2 \tag{1}$$

where m is the characteristic mass and τ is the character time. What should we use for mass? Well we have shown a lot of interest in carbons so far so let's go with that: $m = 12AMU = 12 \times 1.66 \times 10^{-27} kg \approx 10^{-26} kg$, which means that the frequency is approximately

$$\begin{aligned} f = \frac{1}{\tau} &= \frac{1}{r_m} \sqrt{\frac{\epsilon}{m}} \\ &= \frac{1}{1.5 \times 10^{-10} m} \sqrt{\frac{6 \times 10^{-19} J}{10^{-26} kg}} \\ &\approx \frac{\sqrt{6}}{1.5} 10^{13.5} \frac{1}{s} \approx 3 \times 10^{13} Hz && (2) \\ \tau &= 1.9 \times 10^{-14} s \approx 2 \times 10^{-14} s && (3) \end{aligned}$$

2.2 Part b)

Assume a Lennard-Jones potential describes the covalent bond. Find the parameters a and b. Do a Taylor expansion around the equilibrium position to find an effective spring constant and the resulting typical frequency of vibration.

To find a and b, and to do the Taylor expansion, we will need the derivatives of the potential. Let's find them now:

$$\begin{aligned} V(r) &= \frac{a}{r^{12}} - \frac{b}{r^6} && \text{(4a)} \\ V'(r) &= \frac{\partial V}{\partial r} = -12 \frac{a}{r^{13}} + 6 \frac{b}{r^7} && \text{(4b)} \\ V''(r) &= \frac{\partial^2 V}{\partial r^2} = 156 \frac{a}{r^{14}} - 42 \frac{b}{r^8} && \text{(4c)} \\ &\vdots \end{aligned}$$

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So now let's find a and b. We know that at the bond length is the position of the minimum of the potential well *i.e.* $V' = 0$ at $r = r_m$. Therefore,

$$\begin{aligned}
V'(r = r_m) &= 0 \\
&= -12\frac{a}{r_m^{13}} + 6\frac{b}{r_m^{7}} \\
12\frac{a}{r_m^{13}} &= 6\frac{b}{r_m^{7}} \\
b &= \frac{2a}{r_m^{6}}. \qquad (5)
\end{aligned}$$

We also know that the depth of the well at $r = r_m$ is $V = \epsilon$ so then we can find and equation to give a in terms of r_m and ϵ,

$$\begin{aligned}
V(r = r_m) &= -\epsilon \\
&= \frac{a}{r_m^{12}} - \frac{b}{r_m^{6}} \\
&= \frac{a}{r_m^{12}} - \frac{2a}{r_m^{6}}\frac{1}{r_m^{6}} \\
&= -\frac{a}{r_m^{12}},
\end{aligned}$$

which means

$$\begin{aligned}
a &= \epsilon r_m^{12} \qquad (6) \\
b &= \frac{2a}{r_m^{6}} = 2\epsilon r_m^{6}. \qquad (7)
\end{aligned}$$

So we know that the Lennard-Jones potential is

$$\begin{aligned}
V(r) &= \frac{a}{r^{12}} - \frac{b}{r^{6}} \\
&= \epsilon\left(\frac{r_m}{r}\right)^{12} - 2\epsilon\left(\frac{r_m}{r}\right)^{6} \\
&= 4\epsilon\left[\left(\frac{\sigma}{r}\right)^{12} - \left(\frac{\sigma}{r}\right)^{6}\right].
\end{aligned}$$

We have made the convenient definition that $\sigma = 2^{1/6} r_m$. If you ever have to work with the Lennard-Jones potential, you will probably see it in terms of σ

rather than r_m. We can do the expansion about r_m

$$\begin{aligned}
V(r) &\approx V(r=r_m) + V'(r=r_m)r + \frac{1}{2}V''(r=r_m)r^2 + \ldots \\
&\approx -\epsilon + 0 + \frac{1}{2}\left[156\frac{a}{r_m^{14}} - 42\frac{b}{r_m^8}\right]r^2 \\
&= -\epsilon + \frac{1}{2}\left[156\frac{\epsilon r_m^{12}}{r_m^{14}} - 42\frac{2\epsilon r_m^6}{r_m^8}\right]r^2 \\
&= -\epsilon + \frac{1}{2}\left[\frac{156}{r_m^2} - \frac{84}{r_m^2}\right]\epsilon r^2 \\
&= -\epsilon + \frac{1}{2}\left(\frac{72}{r_m^2}\epsilon\right)r^2 \\
V(r) + \epsilon &= \frac{1}{2}kr^2 \qquad (8)
\end{aligned}$$

where I defined an effective spring constant

$$k \equiv \frac{72\epsilon}{r_m^2}. \qquad (9)$$

A harmonic oscillator like this has oscillates at a characteristic frequency which you remember from classical mechanics to be

$$f = \frac{1}{2\pi}\sqrt{\frac{k}{m}} = \frac{1}{-}\sqrt{\frac{72\epsilon}{mr_m^2}} = \frac{1}{2\pi r_m}\sqrt{\frac{72\epsilon}{m}} \qquad (10)$$

$$= 6.97 \times 10^{13} Hz \approx 7 \times 10^{13} Hz \qquad (11)$$

if we use the same m we used previously. Equivalently the characteristic period is

$$\tau = \frac{1}{f} = 1.4 \times 10^{-14} s. \qquad (12)$$

Comparing this to our answer in part a) demonstrates that our dimensional analysis was pretty good.

2.3 Part c)

Estimate the time step required to do a classical mechanics-based simulation of protein dynamics.

If you cannot course-grain the problem and must simulate every atom as a Lennard-Jones bead (often you don't need this much detail) then your time step must be much less than the period of the bead in it's potential. In the previous two sections we found $\tau \approx (1.4 - 2) \times 10^{-14} s$. We'd be pushing it if our time step was only 10 times less than the period. That extreme would say our time step δt should be

$$\delta t < 1 \times 10^{-15} s. \qquad (13)$$

And that's one of the major reasons why simulations of proteins can be so very challenging.

3 Problem 3) Phillips 5.5

3.1 Part a,i)

Consider 1cc of water. Estimate the ratio of multiplicities by using the fact that the latent heat of vapourization is $Q_V = 40.66kJ/mol$ at $373K$.

In the thermodynamic limit (which we're definitely in)

$$dS = \frac{dQ}{T}. \tag{14}$$

We can find dQ (and then dS) by counting the number of water molecules in 1cc of water

$$\begin{aligned} dQ &= NQ_V \\ &= 1cm^3 \left(\frac{g}{cm^3}\right)\left(\frac{mol}{18g}\right) Q_V = Q_V \frac{mol}{18} \\ dS &= \frac{dQ}{T} = Q_V \frac{mol}{18T} = \frac{4.066 \times 10^4 J}{mol} \frac{mol}{18 \times 373K} \\ &= 6.06J/K. \end{aligned} \tag{15}$$

Comparing this macroscopic value for the entropy change with the microscopic form

$$\Delta S = S_G - S_L = k_\mathrm{B} \ln\left(\frac{W_G}{W_L}\right) \tag{16}$$

from which we see that the ratio of multiplicities is

$$\begin{aligned} \frac{W_G}{W_L} &= \exp\left(\Delta S/k_\mathrm{B}\right) \\ &= \exp\left(\frac{6.06J/K}{1.38 \times 10^{-23}J/K}\right) = \exp\left(4.39 \times 10^{23}\right) \\ &= 10^{4.39\times 10^{23}/\ln 10} = 10^{1.9\times 10^{23}}. \end{aligned} \tag{17}$$

That's big. Very big.

3.2 Part a,ii)

What change of volume is needed to account for this change in number of states? Is that change reasonable?

We have the relation between the numbers of states W and the volume occupied V

$$\frac{W_G}{W_L} = \left(\frac{V_G}{V_L}\right)^N \tag{18}$$

where N is the number of molecules. For 1cc of water

$$\begin{aligned} N &= 1cm^3 \left(\frac{g}{cm^3}\right)\left(\frac{mol}{18g}\right)\left(\frac{6.24 \times 10^{23}}{mol}\right) \\ &= 3.3 \times 10^{22}. \end{aligned}$$

So then the predicted change in volume is

$$\begin{aligned}\frac{V_G}{V_L} &= \left(\frac{W_G}{W_L}\right)^{1/N} \\ &= \left(10^{1.9\times10^{23}}\right)^{1/3.3\times10^{22}} = 570000 = 6\times10^{5}.\end{aligned} \tag{19}$$

That's a pretty big expansion. Intuitively, we may want to say it doesn't make sense but let's stop for a moment and consider some properties of vapour and water. First off (just to be super clear) the mass of a water molecule obviously doesn't change and neither does the number of molecules. So a change in volume is a change in density

$$\frac{V_G}{V_L} = \frac{\rho_L}{\rho_G}. \tag{20}$$

We all know the density of water is $\rho_L = 1g/cm^3$. If you look up the density of vapour at atmosphere you will find $\rho_G = 5.96 \times 10^{-4} g/cm^3$. So then experimentally

$$\frac{\rho_L}{\rho_G} = \frac{1g/cm^3}{5.96\times10^{-4}g/cm^3} = 1700. \tag{21}$$

We're off by two orders of magnitude but not as bad as maybe we thought we were at first glance. It seems that something more than just an ideal gas of non-interacting molecules is needed as a model for either (or both) liquid water and water vapour.

4 Problem 4) Phillips 6.1

4.1 Part a,i)

How many disulfide pairing arrangements are possible between 6 cysteines? Let $n = 6$.

- The first pair can be made between any of them so you have $(n-1) = 5$ options.
- The next pair can't involve the two cysteines that already formed the first pair. It can only be made with any of the $(n-3) = 3$ left over cysteines.
- This last pair has only a single $(n-5) = 1$ option. The last two must pair up.

So the number of arrangements is simply

$$W = (n-1)(n-3)(n-5) = 5\times3\times1 = 15. \tag{22}$$

4.2 Part a,ii)

Derive the general formula for any number of cysteines. The pattern for the number of arrangements is already pretty clear from part a,i) since it was written in terms of n. If $n > 6$ we could have just kept on going

$$\begin{aligned} W &= (n-1)(n-3)(n-5)(n-7)(n-9)\ldots \\ &= \prod_{i=1,\ \mathrm{odd}}^{n} (n-i)\,. \end{aligned} \tag{23a}$$

where we're only interested in **odd** i-values. If you don't like this, you can change the form of the product sequence so that i runs over all integers to n:

$$W = \prod_{i=0}^{n/2} (n - [2i+1]) \tag{23b}$$

but now n must be even (Philips mentions this criteria in the question).

A third form is also acceptable

$$W = \frac{n!}{2^{n/2}\,(n/2)!}\,. \tag{23c}$$