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Chapter 2

Biological Structures: Rulers at Many Different Scales

2.1 Revisiting the *E. coli* mass

We made a simple estimate of the mass of an *E. coli* cell by assuming that such cells have the same density of water. However, a more reasonable estimate is that the density of the macromolecules of the cell is 1.3 times that of water (BNID 101502, 104272). As a result, the estimate of the mass of an *E. coli* cell is off by a bit. Using that two-thirds of the mass is water and that the remaining one-third is macromolecular, compute the percentage error made by treating the macromolecular density as the same as that of water.

Our approximate estimate gives a mass of *E. coli* of

$$M_{E.coli}^{approx} = \rho_{water} V_{E.coli}. \tag{2.25}$$

The better estimate is built by noting

$$M_{E.coli} = \frac{2}{3}\rho_{water} V_{E.coli} + \frac{1}{3} 1.3 \rho_{water} V_{E.coli}. \tag{2.26}$$

This can be simplified to

$$M_{E.coli} \approx \frac{3.3}{3} M_{E.coli}^{approx} \approx 1.1 M_{E.coli}^{approx}, \tag{2.27}$$

which tells us that we make roughly a 10% error by using the density of water rather than the correct macromolecular density.

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2.2 A feeling for the numbers: the chemical composition of a cell by pure thought

Make an estimate of the composition of carbon, hydrogen, oxygen, and nitrogen in the dry mass of a bacterium. Using knowledge of the size and mass of a bacterium, the fraction of that mass that is "dry mass" (that is, $\approx 30\%$) and the chemical constituents of a cell, figure out the approximate small integers (<10) for the composition $C_mH_nO_pN_q$, that is, find m, n, p, and q.

If we average the number of C, H, O, and N atoms in all the side chains of the 20 amino acids, we find C = 3, H = 6, N = $\frac{1}{2}$, and O = $\frac{1}{2}$. The main chain has C=2, H=2 (2 lost during peptide bond formation), N=1, O=1 (1 lost during peptide bond formation). This gives us the general formula for peptides of $C_5H_8O_2N_2$.
If we make a similar estimate for the base pairs, sugars, and lipids (taking phosphatidylethanolamine with 16C lipid tails as a representative lipid, we find the approximate formulae, $C_9H_{11}O_6N_4$, $C_5H_{10}O_5$, and $C_5H_{10}O_1$, respectively.

Now, what is the ratio of the different constituents? From Table 2.1 we know there are about 2.4×10^6 protein molecules. Assuming an average protein content of 300 amino acids we then get about 7×10^8 amino acids. How does this number compare to the number of bases or phospholipids in the cell? From the table we see that all the different classes of RNA sum to roughly 3×10^5 RNA molecules. Let's make the overestimate that each of these molecules is about 1000 bases. Combining this with the DNA content from the genome itself, we then get the equivalent of 10^8 base pairs in the cell. As a result we see the nucleic acids are only a small component of the chemical composition of the cell with respect to amino acids. Finally, this is also the case for phospholipids, as there are only about 2×10^7 molecules in the cell. As a result we conclude that the chemical composition of the cell is closest to that of amino acids: $C_5H_8O_2N_2$.

An alternative way to see this same result is based upon the relative masses contributed by each of these classes of molecules. We know that half of the dry mass of the cell is protein, so protein will get a weight of $\frac{1}{2}$. There is 3 times more protein than DNA and RNA, so DNA+RNA will get a weight of $\frac{1}{6}$. We will assume that the rest of the dry mass is sugar and lipids, and we assign them each a weight of $\frac{1}{6}$. This gives us a general formula of $C_5H_8O_2N_2$, which is the general formula for the peptides.

2.3 A feeling for the numbers: microbes as the unseen majority

(a) Use Figure 2.1 to justify the assumption that a typical bacterial cell (that is, *E. coli*) has a surface area of $6\,\mu\text{m}^2$ and a volume of $1\,\mu\text{m}^3$. Also, express this volume in femtoliters. Make a corresponding estimate of the mass of such a bacterium.
(b) Roughly 2–3 kg of bacteria are harbored in your large intestine. Make an estimate of the total number of bacteria inhabiting your intestine. Estimate

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the total number of human cells in your body and compare the two figures. **(c)** The claim is made (see Whitman et al., 1998) that in the top 200 m of the world's oceans, there are roughly 10^{28} prokaryotes. Work out the total volume taken up by these cells in m^3 and km^3. Compute their mean spacing. How many such cells are there per milliliter of ocean water?

(a) *E. coli* has (roughly) the shape of a cylinder that is 2 μm in length and 0.5 μm in radius. For those that are so inclined, the bacterium can alternatively be treated as a spherocylinder, though the results will not change in any interesting way. Using these numbers we calculate the area of an *E. coli* to be:

$$A_{cell} = \pi \times 1\ \mu\text{m} \times 2\ \mu\text{m} \approx 6\ \mu\text{m}^2. \tag{2.28}$$

Its volume is:

$$V_{\text{cell}} = \pi \times \left(\frac{1}{2}\,\mu\text{m}\right)^2 \times (2\,\mu\text{m}) \approx 1\,\mu\text{m}^3 \tag{2.29}$$

$$= 1\,\text{fL}. \tag{2.30}$$

If we assume that the density of a bacterium is the same as that of water, the mass of one bacterium is $10^3\text{kg/m}^3 \times 10^{-18}\ \text{m}^3 \approx 10^{-15}$ kg = 1 pg.

(b) The fact that each bacterium has a mass of 1 pg implies that $2-3$ kg worth of bacteria in the intestines of one person amounts to $2 \sim 3 \times 10^{15}$ bacteria.

Assume that the size of a typical human cell is roughly 10 μm in diameter and has a spherical shape with the same density as that of water. Let's assume that the mass of a "typical" human body is roughly 80 kg. Further, let's assume that thirty percent of the human mass corresponds to cells. On the basis of these assumptions, we find that the number of the cells in a human body is approximately

$$\frac{M_{\text{human}}}{V_{\text{cell}}\rho_{H_2O}} = \frac{\frac{1}{3} \times 80\ \text{kg}}{4/3\pi \times (5 \times 10^{-6}\ \text{m})^3 \times 1000\ \text{kg/m}^3} \simeq 5 \times 10^{13}. \tag{2.31}$$

By this estimate, the number of bacterial cells outnumbers the number of human cells by more than a factor of ten.

(c) Using (a) we can estimate the volume of 10^{28} prokaryotes to be about $10^{-18}\,\text{m}^3 \times 10^{28} = 10^{10}\,\text{m}^3$, which is equal to $10\,\text{km}^3$.

The number density of these cells can be obtained on the basis of the estimate that 2/3 of the surface of the Earth is covered with water. Given the radius of the Earth of approximately 6400 km, this corresponds to an area of roughly $3 \times 10^{14}\ \text{m}^2$. Hence, the volume of water occupied by these 10^{28} prokaryotes in the top 200 m of the ocean is roughly $7 \times 10^{16}\ \text{m}^3$ or 7×10^{19} L. As a result, the concentration of prokaryotes is roughly 10^5/mL. Using the formula that the mean spacing is given as $d = c^{-1/3}$, one finds a mean spacing between these cells of roughly 200 μm.

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2.4 A feeling for the numbers: molecular volumes and masses

(a) Estimate the volumes of the various amino acids in units of nm^3.
(b) Estimate the mass of a "typical" amino acid in daltons. Justify your estimate by explaining how many of each type of atom you chose. Compare your estimate with the actual mass of several key amino acids such as glycine, proline, arginine, and tryptophan.
(c) On the basis of your result for part (b), deduce a rule of thumb for converting the mass of a protein (reported in kDa) into a corresponding number of residues. Apply this rule of thumb to myosin, G-actin, hemoglobin, and hexokinase and compare your results with the actual number of residues in each of these proteins. Relevant data for this problem are provided on the book's website.

(a) As a simple approximation, consider the glycine residue as a cylinder. By measuring the dimensions of glycine as revealed in its PDB file, we find its length is roughly 0.7 nm and the radius is about 0.16 nm. The volume of glycine is: $V_{glycine} = 0.7 \cdot \pi \cdot 0.16^2 \simeq 0.056$ nm^3. Notice, then the typical volume of amino acids is

$$M_{glycine} = 57 \text{ Da}$$

$$V_{typical} = \frac{V_{glycine}}{M_{glycine}} \cdot M_{typical} = \frac{0.056}{57} \cdot 110 \simeq 0.108 \text{ nm}^3$$

$$\text{RULE} \rightarrow V_{protein}(\text{nm}^3) = \frac{M_{protein}(kDa)}{110Da} \cdot 0.108$$

If you want to use actual PDB files of amino acids to calculate their volumes you'll have to look around on the Internet. A simple Google search for "amino acid pdb" should give you plenty of relevant pages. One useful on, for example, is `http://wbiomed.curtin.edu.au/teach/biochem/tutorials/pdb/index.html`. These coordinates can also be found on the book website.

(b) By averaging all the side chains of the 20 amino acids, we can get the number of C, H, O, N atoms. The result is C$\simeq$ 3, H$\simeq$ 6, N$\simeq$ 1/2 and O$\simeq$ 1/2. The main chain has C=2, H=2 (lose 2 in forming peptide), N=1, O=1 (lose 1 in forming peptide). Then there are two choices for calculating the typical size of an amino acid: C=5, H=8, N=2, O=1 (112 Da) or C=5, H=8, N=1, O=2 (114 Da). Either way gives us a mass of roughly 110 Daltons. If including the backbone of the peptide, the amino acids will each gain 18 Daltons due to the addition of H_2O to the molecule.

Amino Acid	glycine	proline	arginine	tryptophan
Mass (Da)	57	98	157	186

(c) The rule: The number of amino acids= $\frac{M_{protein}(Da)}{110\text{Da}}$.

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Name	Estimated number of aa	Actual number of aa
Myosin	4727	~ 3500
G-actin	381	375
Hemoglobin (human)	586	574
Hexokinase (yeast)	927	972

Calculate % error to compare the estimated versus actual number.

Myosin % error: 35%
G-actin: 1.6%
Hemoglobin: 2%
Hexokinase (yeast): 4.6%

The rule works well for 3 out of 4 proteins.

2.5 Minimal media and *E. coli*

Minimal growth medium for bacteria such as *E. coli* includes various salts with characteristic concentrations in the mM range and a carbon source. The carbon source is typically glucose and it is used at 0.5% (a concentration of 0.5 g/100 mL). For nitrogen, minimal medium contains ammonium chloride (NH_4Cl) with a concentration of 0.1 g/100 mL.
(a) Make an estimate of the number of carbon atoms it takes to make up the macromolecular contents of a bacterium such as *E. coli*. Similarly, make an estimate of the number of nitrogens it takes to make up the macromolecular contents of a bacterium? What about phosphate?
(b) How many cells can be grown in a 5 mL culture using minimal medium before the medium exhausts the carbon? How many cells can be grown in a 5 mL culture using minimal medium before the medium exhausts the nitrogen? Note that this estimate will be flawed because it neglects the *energy* cost of synthesizing the macromolecules of the cell. These shortcomings will be addressed in Chapter 5.

(a) A standard *E. coli* cell is composed of approximately 3×10^6 proteins, 4×10^6 base pairs, and 2×10^7 lipids. These numbers are consistent with the numbers given in the chapter as well as those found in Table 1 of *Physiology of the Bacterial Cell* by Neidhardt, Ingraham and Schaecter. To determine the number of sugars needed to make a bacterium, we need to know how many carbon atoms are in a typical protein, a DNA base pair, and a standard lipid. For this problem we will say that, on average, each amino acid has 5 carbon atoms, each sugar + base pair has 20 carbon atoms, and each lipid has 40 carbon atoms. Of course, these are all crude estimates and as with the entirety of the solution for this problem, should be seen as a simple estimate to give a feeling for the numbers. Given these numbers, the amount of carbon in each type of

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molecule is:

$$\begin{aligned} 3 \times 10^6 \text{ proteins} \cdot \frac{300\,\text{amino acids}}{\text{protein}} \cdot \frac{5\,\text{carbons}}{\text{amino acid}} &= 4.5 \times 10^9 \text{carbon atoms} \\ 4 \times 10^6 \text{ base pairs} \cdot \frac{20\,\text{carbons}}{\text{base pair}} &= 8 \times 10^7 \text{ carbon atoms} \\ 2 \times 10^7 \text{ lipids} \cdot \frac{40\,\text{carbons}}{\text{phospholipid}} &= 8 \times 10^8 \text{ carbon atoms.} \end{aligned}$$

We see that most of the carbon of a cell is invested in its proteins and we can neglect the contributions from DNA and lipids. Then we have about 5×10^9 carbon atoms in an *E. coli* cell and since one glucose molecule is made up of 6 carbons we can calculate the minimum number of glucose molecules that must be metabolized to make a single *E. coli* cell:

$$5 \times 10^9 \text{ carbons} \cdot \frac{1\,\text{sugar}}{6\,\text{carbons}} \approx 10^9 \text{ sugar molecules.}$$

In the case of nitrogen, given problems 2.2 and 2.4 we know we have about two nitrogen atoms per amino acid. We also know that each base pair has about eight nitrogen atoms. Finally, phospholipid molecules usually have one nitrogen atom. As a result, the number of nitrogen atoms corresponding to each macromolecule is

$$\begin{aligned} 3 \times 10^6 \text{ proteins} \cdot \frac{300\,\text{amino acids}}{\text{protein}} \cdot \frac{2\,\text{nitrogen atoms}}{\text{amino acid}} &= 2 \times 10^9 \text{nitrogen atoms} \\ 4 \times 10^6 \text{ base pairs} \cdot \frac{8\,\text{nitrogen atoms}}{\text{base pair}} &= 3 \times 10^7 \text{ nitrogen atoms} \\ 2 \times 10^7 \text{ lipids} \cdot \frac{1\,\text{nitrogen atoms}}{\text{phospholipid}} &= 2 \times 10^7 \text{ nitrogen atoms.} \end{aligned}$$

As a result, the number of nitrogen atoms in the macromolecules of the bacterial cell is about 2×10^9.

Finally, each DNA base pair has two phosphate atoms, while each lipid molecule has one. As a result, the amount of phosphate in the cell's macromolecules is

$$\begin{aligned} 4 \times 10^6 \text{ base pairs} \cdot \frac{2\,\text{phosphate atoms}}{\text{base pair}} &= 8 \times 10^6 \text{ nitrogen atoms} \\ 2 \times 10^7 \text{ lipids} \cdot \frac{1\,\text{phosphate atom}}{\text{phospholipid}} &= 2 \times 10^7 \text{ nitrogen atoms.} \end{aligned}$$

Which means that the total amount of phosphate in macromolecules is about 3×10^7.

(b) As noted in the statement of the problem, the glucose is present in the medium at a concentration of 0.5g/100 mL. This implies that in 5 mL of minimal media, there are about 10^{-2} g of glucose. How many sugar molecules is this?

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Since the formula for glucose is $C_6H_{12}O_6$, the molecular mass is 180 Da. Hence, the number of sugars is

$$\#\ \text{sugars} \approx \frac{10^{-2}\ \text{g}}{180\ g/6 \times 10^{23}\ \text{molecules}} \approx 3 \times 10^{19}\ \text{glucose molecules.} \quad (2.32)$$

According to our estimate from part (a) (flawed though it is because it emphasizes only the construction material cost of making a cell and ignores the energetic requirements), it takes 10^9 sugar molecules to make a bacterium and hence our 5 mL culture can support roughly 10^{10} bacteria. This is consistent with our intuition because a saturated culture has roughly 10^9 cells/mL.

The molecular mass of NH_4Cl is about 50 Da. This means that in 5 mL of culture we have 6×10^{19} nitrogen atoms. As a result, if nitrogen was the limiting building block our culture would be able to support 3×10^{10} cell. From our estimations, when our culture starts running out of its carbon source it will also start running out of its nitrogen source.

Just to reiterate, the point of this estimate is to get a sense of the cellular inventory and how it relates to the molecular contents of the growth medium that is used for those cells. The precise numbers should not be taken too seriously.

2.6 Atomic-level representations of biological molecules

(a) Obtain coordinates for several of the following molecules: ATP, phosphatidylcholine, B-DNA, G-actin, the lambda repressor/DNA complex or Lac repressor/DNA complex, hemoglobin, myoglobin, HIV gp120, green fluorescent protein (GFP), and RNA polymerase. You can find the coordinates on the book's website or by searching in the Protein Data Bank and various other Internet resources.
(b) Download a structural viewing code such as VMD (University of Illinois), Rasmol (University of Massachusetts), or DeepView (Swiss Institute of Bioinformatics) and create a plot of each of the molecules you downloaded above. Experiment with the orientation of the molecule and the different representations shown in Figure 2.32.
(c) By looking at phosphatidylcholine, justify (or improve upon) the value of the area per lipid ($0.5\,\text{nm}^2$) used in the chapter.
(d) Phosphoglycerate kinase is a key enzyme in the glycolysis pathway. One intriguing feature of such enzymes is their enormity in comparison with the sizes of the molecules upon which they act (their "substrate"). This statement is made clear in Figure 5.5 (p. 294). Obtain the coordinates for both phosphoglycerate kinase and glucose and examine the relative size of these molecules. The coordinates are provided on the book's website.

(a) The following are the PDB accession number of the molecules used in this problem or the link to the relevant websites. All of them are also available on the book website.

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- ATP: `ATP.pdb` from `http://xray.bmc.uu.se/hicup`.
- Phosphatidylcholine: `stearyl-oleyl-phophacholine.pdb` from `http://faculty.gvsu.edu/carlsont/mm/lipids/pg.html`.
- B-DNA: `bdna.pdb` from `http://chemistry.gsu.edu/glactone/PDB/pdb.html`.
- G-actin: `1J6Z.pdb` from the PDB.
- Lambda repressor/DNA complex: `1LMB.pdb` from the PDB has the DNA-binding region of lambda repressor complexed with DNA.
- Lac repressor/DNA complex: `1lbg.PDB` and `1tfl.pdb` from the PDB.
- Hemoglobin: `1hga.pdb` from the PDB.
- Myoglobin: `1mbo.pdb` from the PDB.
- HIV gp120: `1GC1.PDB` from the PDB.
- Green fluorescent protein (GFP): `1GFL.pdb` from the PDB.
- RNA polymerase: `1L9U.pdb` from the PDB.

(b) Crystal structures can be displayed in a variety of ways. All the figures here were generated using Jmol version 11.4. Figures 2.38, 2.39, and 2.42 are "ball-and-stick" representations. The hydrogens are not shown, which is often the case, and the rest of the atoms are color coded such that grey corresponds to carbon, red to oxygen, blue to nitrogen, and orange to phosphate (see fig. 2.38). Figures 2.40, 2.43, 2.44, and 2.45 are generally called ribbon-diagrams or, in Jmole, the representation "scheme" is "cartoon." Ribbon diagrams help make sense of complex protein structures because they can reduce the molecule to its secondary structural motifs, such as α-helices and β-sheets. Figures 2.48 and 2.46 are space-filling representations, in which each atom is marked by its equivalent Van der Waals sphere, the diameter of which are generally roughly 2.5 $\AA$ (see fig. 2.48B). Space-filling models have the same color-coding scheme as the ball-and-stick diagrams. The wiry representation in figure 2.41 is called a "trace" in Jmol. These and other kinds of representations are listed in Jmol under Schemes in the Style menu.

(c) Fig. 2.48 shows that the effective cross section of a phosphatidylcholine polar head is roughly a square with a side of 0.5 nm. This results in an area of 0.25 nm^2, very close to the value of 0.5 nm^2 used in the chapter.

(d) See fig. 2.49.

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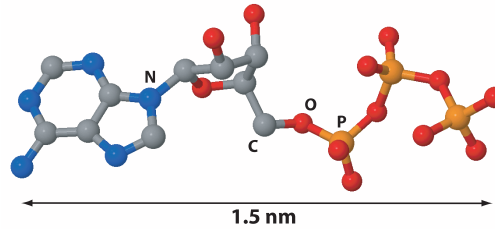

Figure 2.38: A crystal structure of adenosine-triphosphate (atp.pdb). The three phosphates PO_4 are on the right and the rest is adenosine. ATP is the energy currency of the cell. Most reactions that require energy obtain it from one of the bonds of this molecule, hydrolizing ATP to ADP.

2.7 Coin flips and partitioning of fluorescent proteins

In the estimate on cell-to-cell variability in the chapter, we learned that the standard deviation in the number of molecules partitioned to one of the daughter cells upon cell division is given by

$$\langle n_1^2 \rangle - \langle n_1 \rangle^2 = Npq. \tag{2.33}$$

(a) Derive this result.
(b) Derive the simple and elegant result that the average difference in intensity between the two daughter cells is given by

$$\langle (I_1 - I_2)^2 \rangle = \alpha I_{\text{tot}}, \tag{2.34}$$

where I_1 and I_2 are the intensities of daughters 1 and 2, respectively, and I_{tot} is the total fluorescence intensity of the mother cell and assuming that there is a linear relation between intensity and number of fluorophores of the form $I = \alpha N$.

(a) The number of ways we can divide N indistinguishable molecules into two cells is given by:

$$W = \frac{N!}{n_1!(N - n_1)!}, \tag{2.35}$$

where N is a total number of molecules and n_1 is the number of molecules that went to daughter cell 1. The probability of a particular sequence of N molecules going to daughter cell 1 and daughter cell 2, where the probability of the molecule going to daughter cell 1 is p and to daughter cell 2 is q, is

$$p^{n_1} q^{N - n_1}, \tag{2.36}$$

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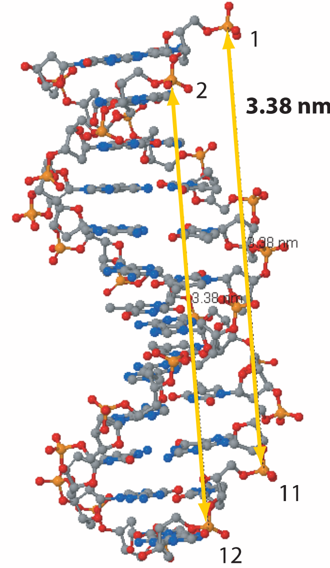

Figure 2.39: A crystal structure of 12 base pairs of DNA in B-form (bdna.pdb). B-DNA is double stranded DNA in the form usually found in *in vivo* conditions. There are 10 base pair intervals from the 1st to 11th and 2nd to 12th base pairs. By measuring the distances between the corresponding phosphates on the same backbone (there are two phosphate backbones) one can see the canonical base pair spacing of 0.34 nm. This only works because the helical periodicity is nearly 10 bp. Because of the coiling of the helix, the distance between two adjacent phosphates is 0.65 nm.

since if n_1 molecules went to daughter cell 1, $N - n_1$ molecules had to go to cell 2. Thus, the probability distribution is given by

$$P(n_1, N) = \frac{N!}{n_1!(N-n_1)!} p^{n_1} q^{N-n_1}. \tag{2.37}$$

To get the average number of molecules going to daughter cell 1, we have to sum over all the configurations. In particular, we have

$$\langle n_1 \rangle = p \frac{\partial}{\partial p} \sum_{n_1=0}^{N} \frac{N!}{n_1!(N-n_1)!} p^{n_1} q^{N-n_1}. \tag{2.38}$$

We can calculate the second moment of the distribution similarly as

$$\langle n_1^2 \rangle = p \frac{\partial}{\partial p} p \frac{\partial}{\partial p} \sum_{n_1=0}^{N} \frac{N!}{n_1!(N-n_1)!} p^{n_1} q^{N-n_1} \tag{2.39}$$

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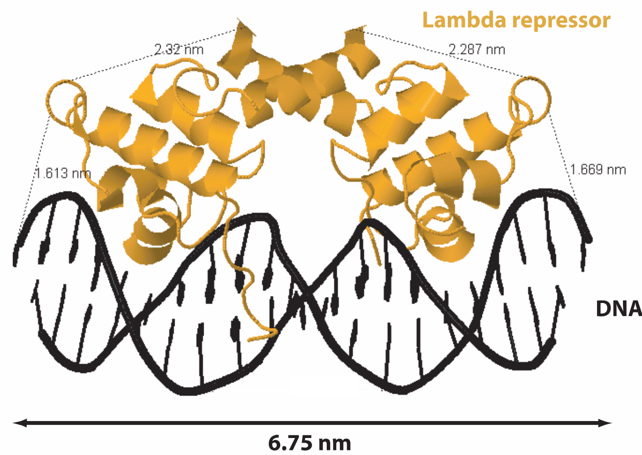

Figure 2.40: A crystal structure of the DNA-binding domain of lambda repressor complexed with DNA (1LMB.pdb). This protein is the main actor in the lambda switch, which is the mechanism by which lambda phage decides whether to lyse its host cell or grow with it in lysogenic growth. Lambda repressor is usually found as a dimer and can either repress or activate transcription.

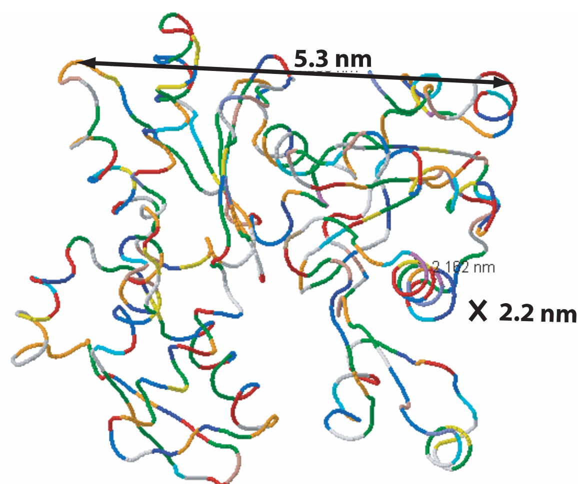

Figure 2.41: A crystal structure of a G-actin (1J6Z.pdb), which is the monomeric unit of actin filaments. These filaments are responsible for cell motility in most eukaryotes. The coil next to the **x** is an α-helix that spans the thickness of the molecule and is roughly 2.2 nm long. The coloring scheme is set to distinguish adjacent amino acid residues.

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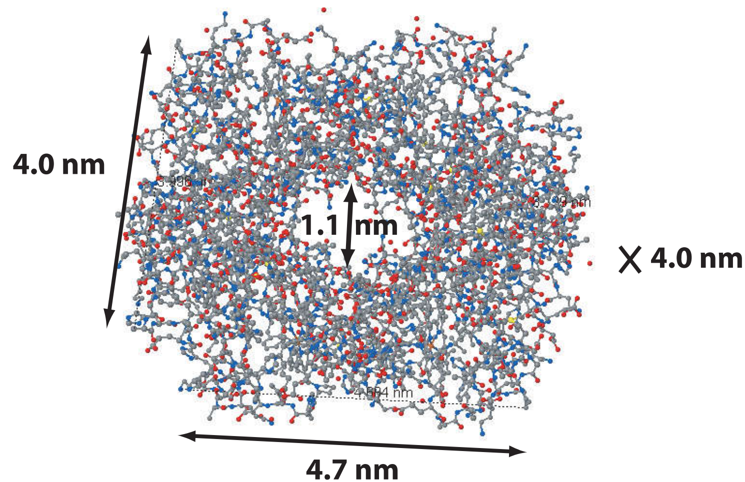

Figure 2.42: Crystal structure of hemoglobin (1hga.pdb), which is the protein that binds oxygen in red blood cells so that it can be transported to other tissues. The **x** on the right indicates that an arrow into the page would show the thickness to be 4 nm. So the rough overall shape of the molecule is a box with dimensions $5 \times 4 \times 4$ nm with a 1 nm hole in the center.

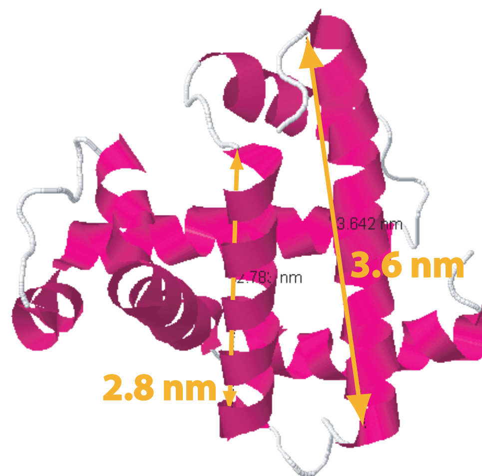

Figure 2.43: Crystal structure of oxymyoglobin (1mbo.pdb). The pink ribbons correspond to α-helix secondary structure motifs and the wires to linkers between them. Oxymyoglobin is myoglobin with a bound oxygen, and it is the molecule that gives fresh meat its red color. Conversion of myoglobin to oxymyoglobin occurs rapidly after slaughter and exposure to air. Conversion of oxymyoglobin to metmyoglobin occurs more slowly and turns the meat brown.

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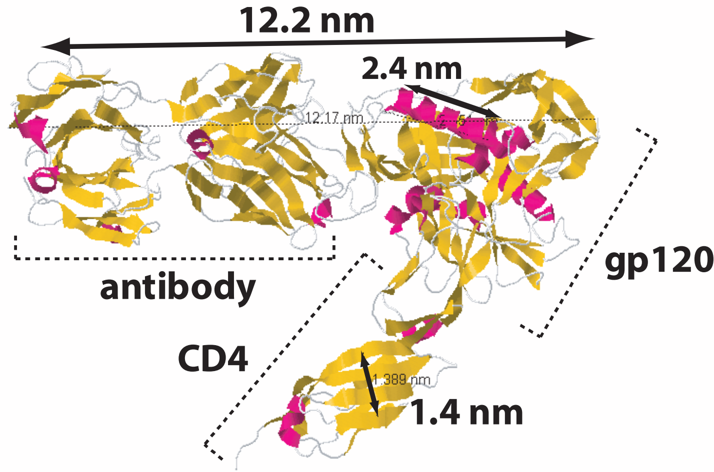

Figure 2.44: Crystal structure of gp120 complexed with CD4 and a neutralizing human antibody (1gc1.pdb). GP120 is an infamous protein expressed by HIV. It allows the virus to enter human immune system helper T-cells by interacting with their CD4 receptor. The antibody in this structure presumably prevents this interaction. One can see from this angle that the overall shape of the complex is a V that nearly lies in a plane; a top down view would reveal a thickness of roughly 3 nm throughout. The pink ribbons correspond to α-helices, the orange bunches of arrows to β-sheets, and the white wires to the chains of amino acids linking them.

Now, we can calculate the difference between the second and the square of the first moment of the distribution as

$$< n_1^2 > - < n_1 >^2 = \left(p\frac{\partial}{\partial p}\left(p\frac{\partial}{\partial p}\sum_{n_1=0}^{N} P \right)\right) - \left(p\frac{\partial}{\partial p}\sum_{n_1=0}^{N} P \right)^2 . \tag{2.40}$$

To rewrite this in a more useful form, we recall the binomial theorem, namely

$$(p+q)^N = \sum_{n_1=0}^{N} \frac{N!}{n_1!(N-n_1)!} p^{n_1} q^{N-n_1} \tag{2.41}$$

and we get

$$\begin{aligned} < n_1^2 > - < n_1 >^2 &= p\frac{\partial}{\partial p}\left(p\frac{\partial}{\partial p}(p+q)^N \right) - (p\frac{\partial}{\partial p}(p+q)^N)^2 \\ &= p\frac{\partial}{\partial p}\left(pN(p+q)^{N-1} \right) - (pN(p+q)^{N-1})^2 \\ &= pN(p+q)^{N-1} + p^2N(N-1)(p+q)^{N-2} \\ &\quad - p^2N^2(p+q)^{2N-2} \end{aligned} \tag{2.42}$$

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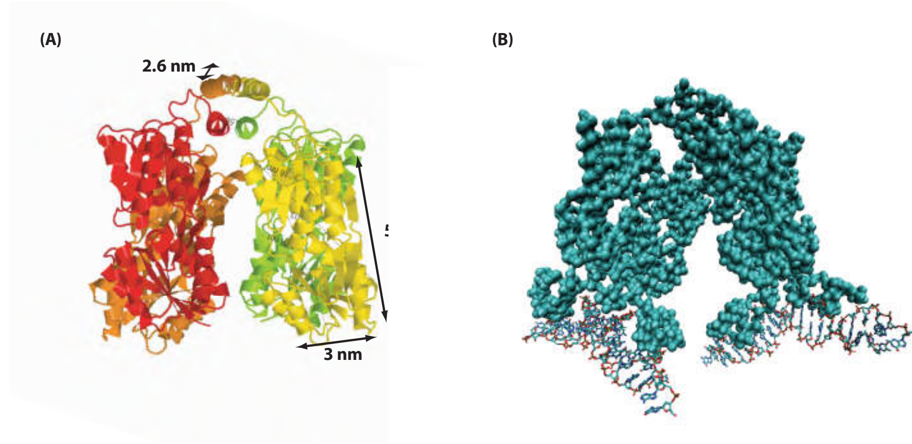

Figure 2.45: Crystal structure of *E. coli* lac repressor. (A) The molecule (1tlf.pdb) is a tetramer, composed of four identical subunits, each of which is marked by a different color. The dimensions of each subunit roughly correspond to a cylinder of length 5 nm and diameter 3 nm. The DNA binding domains are at the top and the subunits are linked together in the bundle of α-helices at the bottom, each of which are 2.6 nm long. (B) Structure 1lbg.pdb shows the tetramer bound to its operator DNA.

Now we use the fact that $p+q=1$ resulting in

$$\begin{aligned} < n_1^2 > - < n_1 >^2 &= pN + p^2N(N-1) - p^2N^2 \\ &= pN + p^2N^2 - p^2N - p^2N^2 \\ &= pN - p^2N = pN(1-p) = Npq \end{aligned} \tag{2.43}$$

(b) These ideas can now be used to examine the relation between the intensities of the two daughter cells and their mother. First, we observe that

$$\langle (I_1 - I_2)^2 \rangle = \langle (2I_1 - I_{tot})^2 \rangle, \tag{2.44}$$

where we have used the fact that $I_1 + I_2 = I_{tot}$. If we expand the binomial and use the relation $I = \alpha N$, this implies

$$\langle (I_1 - I_2)^2 \rangle = 4\alpha^2 \langle N_1^2 \rangle - 4I_{tot}\alpha \langle N_1 \rangle + I_{tot}^2. \tag{2.45}$$

From the previous part of the problem, for the case in which $p = q = 1/2$, we have

$$\langle N_1 \rangle = \frac{N}{2} \tag{2.46}$$

and

$$\langle N_1^2 \rangle = \frac{N}{4} + \frac{N^2}{4}. \tag{2.47}$$

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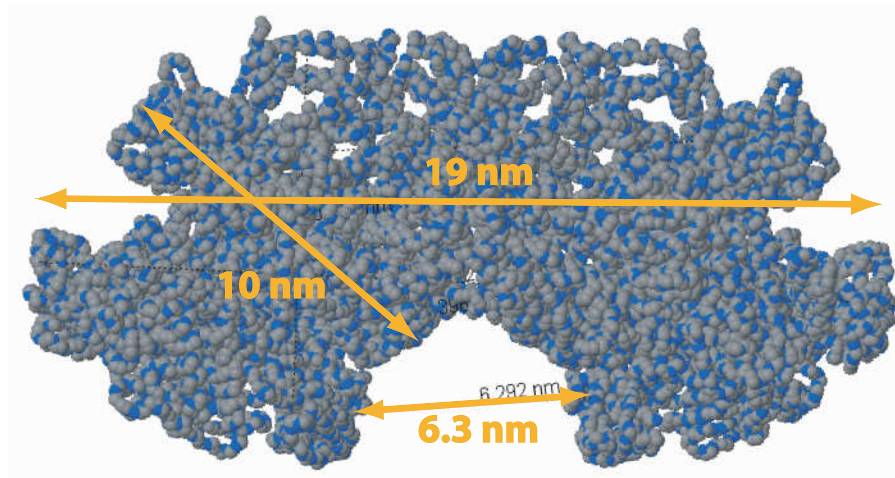

Figure 2.46: Crystal structure of *Thermus Aquaticus* RNA polymerase holoenzyme (1l9u.pdb), which is the molecular machine in charge of translating the message on the DNA to messenger RNA (mRNA). Holoenzyme refers to the complete form of the enzyme, in which all the subunits have assembled. In bacteria RNAP is enough to start this transcription. However, in eukaryotes, the coordinated action of tens of other molecules are needed. *Thermus Aquaticus* is the species of bacterium famous for its thermostable DNA polymerase, which made PCR possible. The shape of the enzyme is roughly that of a bent rod with 10 nm diameter.

As a result, we have

$$\langle (I_1 - I_2)^2 \rangle = \alpha^2 N = \alpha I_{tot}, \tag{2.48}$$

as we set out to prove. This observation is the basis of a very clever scheme for counting proteins.

2.8 HIV estimates

(a) Estimate the total mass of an HIV virion by comparing its volume with that of an *E. coli* cell and assuming they have the same density.
(b) The HIV maturation process involves proteolytic clipping of the Gag polyprotein so that the capsid protein CA can form the shell surrounding the RNA genome and nucleocapsid NC can complex with the RNA itself. Using Figures 2.30 and 2.31 to obtain the capsid dimensions, estimate the number of CA proteins that are used to make the capsid and compare your result with the total number of Gag proteins.

(a) As discussed in the text and as is evident in the electron micrographs of fig. 2.31(B), the HIV virion is spherical with diameter 130 nm. Its volume is then

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Figure 2.47: Crystal structure of green fluorescent protein or GFP (1GFL.pdb), which was obtained originally from bioluminescent jellyfish and is now widely used as a reporter of gene expression. It consists of two β-sheet barrels enclosing α-helices. The barrel on the left we are looking at top-down; so that we can see its diameter of roughly 3 nm. The barrel on the right we see from the side.

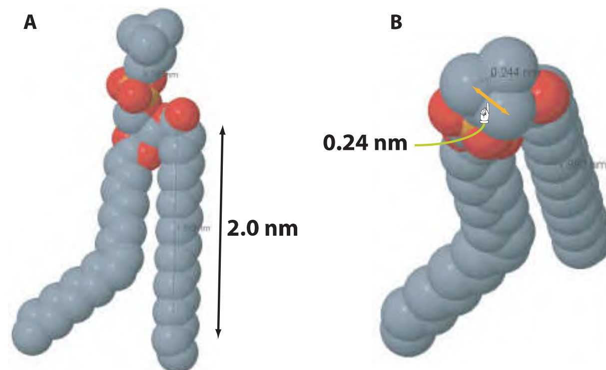

Figure 2.48: Two "space filling" views of a phosphatidylcholine crystal structure (stearyl-oleyl-phophacholine.pdb). Phosphatidylcholine is a lipid commonly found in the membranes of cells. (A) A view of the lipid from the side. The long carbon chains would be embedded inside the membrane and the head at the top would be on the surface. (B) A top down view of the head of the lipid.

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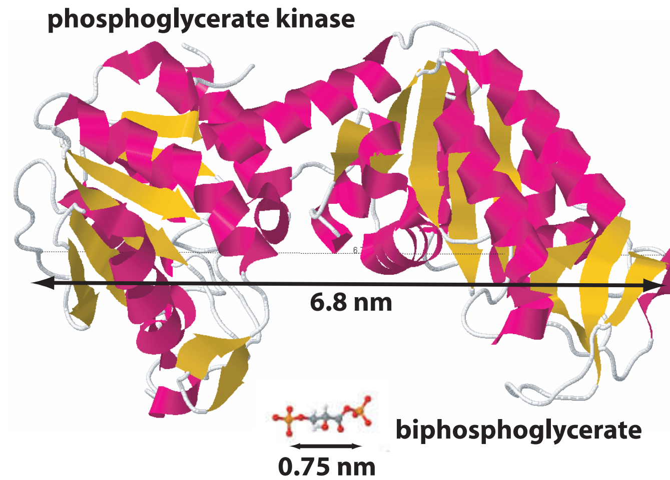

Figure 2.49: Crystal structures of *E. coli* phosphoglycerate kinase (1ZMR.pdb) and its relatively small substrate biphosphoglycerate (1,3-bisphospho-D-glycerate.pdb). The enzyme catalyzes the seventh step of glycolysis, which is the transfer of a phosphate from biphosphoglycerate to ADP forming ATP and phosphoglycerate (see fig. 5.2 for a schematic of the glycolytic pathway).

$\frac{4}{3}\pi(\frac{130}{2})^3$ nm$^3 \approx 1 \cdot 10^6$ nm$^3 = 10^{-3}$ μm^3. For comparison, an *E. coli* is roughly 1 μm^3 with density nearly that of water, which is 1 g/cm^3 = 1 picogram/μm^3. As a result, the estimated mass of an HIV virion is a femtogram.

(b) In sec. 2.2.4, the GAG polyprotein is approximated as a cylinder with cross-sectional area 4π nm^2. Fig. 2.31(A) shows that the capsid protein CA is a section of this cylinder with the same cross-sectional area. The schematic of the mature virion in fig. 2.31(C) shows that the CA proteins come together to form the capsid with inward pointing "spokes," in the same way that the GAG polyproteins form the initial outer shell of the virion. This means that CA and GAG have the same surface areas per protein. Because the surface area of the capsid is less than that of the virion and because each CA protein is cleaved off a GAG polyprotein, this fact immediately implies that not all the CA proteins can be used up to form the capsid.

From the micrographs, the capsid can be approximated as a cone with base radius $r = 25$ nm and side length $s = 100$ nm. Its surface area is then $\pi r s + \pi r^2 \approx 1 \cdot 10^4$ nm^2, and the number of CA proteins making up the capsid is then roughly $\frac{10^4}{4\pi} \approx 800$ CA proteins. This result can also be obtained by multiplying the ready-made estimate of 3500 total GAG proteins by the ratio of the surface areas

$$\text{GAG proteins total} \cdot \frac{\text{surface area capsid}}{\text{surface area virion}} = 3500 \cdot \frac{10^4 \text{ nm}^2}{4\pi \cdot 60 \text{ nm}^2} \approx 800 \text{ CA proteins in capsid}, \quad (2.49)$$

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where the virion radius used is 60 nm instead of 65 nm because the outer 5 nm of the virion shell are taken up by a lipid bilayer.

2.9 Areas and volumes of organelles

(a) Calculate the average volume and surface area of mitochondria in yeast based on the confocal microscopy image of Figure 2.18(C).
(b) Estimate the area of the endoplasmic reticulum when it is in reticular form using a model for its structure of interpenetrating cylinders of diameter $d \approx 10\,\text{nm}$ separated by a distance $a \approx 60\,\text{nm}$, as shown in Figure 2.25.

(a) The mitochondria in this yeast are shaped like a cylinder with a diameter of 400 nm approximately (which could be the resolution limit of the microscope). The total extension of this cylinder is about 20 μm. This results in a total mitochondrial volume of $\pi(0.2\ \mu\text{m})^2 \times 20\ \mu\text{m} \approx 2.5\ \mu\text{m}^3$. The total area is $2\pi \times 0.2\ \mu\text{m} \times 20\ \mu\text{m} \approx 25\ \mu\text{m}^2$.

Mitochondria are thus just a small fraction of the total yeast volume, which is around 500 μm^3.

(b) Each “cross”, the unit that gets repeated in this structure, can be approximated by two cylinders of length a and diameter d. Therefore, its surface area is $2 \times \pi \times 10\ \text{nm} \times 60\ \text{nm} \approx 4000\ \text{nm}^2$. Now, each one of this units occupies a volume $a^3 \approx 0.22 \times 10^{-3}\ \mu\text{m}^3$.

We assume that a fibroblast has a height of approximately 1 μm and, based on figure 2.15, we approximate the area of the fibroblast were the ER is present to be 25 μm^2, around one fourth of the total area of the field of view. Therefore, in this volume of 25 μm^3 we can fit $25\ \mu\text{m}^3/(0.22\times10^{-3}\ \mu\text{m}^3) \approx 10^5$ such units. This in turn corresponds to a total surface area of $10^5 \times 4000\ \text{nm}^2 = 400\ \mu\text{m}^2$.

2.10 An open-ended “feeling for the numbers”: the cell

Using the figures of cells and their organelles provided on the book website, carry out estimates of the following:
(a) The number of nuclear pores in the nucleus of a pancreatic acinar cell.
(b) The spacing between mitochondrial lamellae and the relative area of the inner and outer mitochondrial membranes.
(c) The spacing and areal density of ribosomes in the rough endoplasmic reticulum of a pancreatic acinar cell.
(d) The DNA density in the head of a sperm.
(e) The volume available in the cytoplasm of a leukocyte.

(a) The diameter of the nucleus in this pancreatic acinar cell is 6 μm approximately. We also see that the nuclear pore complexes have a diameter of around 100 nm. There are about 12 nuclear pore complexes in this section. Some of them are marked by the arrows. If we think of this section as a disc of diameter

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6 μm and depth 100 nm this corresponds to a nuclear pore complex density of

$$\frac{12\text{nuclear pore complex}}{\pi \times 6\ \mu\text{m} \times 100\ \text{nm}} \approx 6.4 \frac{\text{nuclear pore complex}}{\mu\text{m}^2}. \tag{2.50}$$

Since the total area of this nucleus is $4\pi \times (6\ \mu\text{m})^2 \approx 450\ \mu\text{m}^2$ this means that on average there are about 3000 nuclear pore complexes on the nuclear membrane.
(b) Lamellae on this mitochondria are spaced every 50 nm. Their average length seems to span the size of the mitochondria, about 600 nm. We think of the mitochondria as a cylinder of 600 nm diameter and 2 μm height. The outer membrane has then an area of

$$A_{\text{out}} = 2 \times \pi \times 0.6\ \mu\text{m} \times 2\ \mu\text{m} \approx 7.5\ \mu\text{m}^2. \tag{2.51}$$

Where the factor of two has been included to account for the fact that this is a bilayer. The inner membrane has basically the same area as the outer membrane plus the contribution from the lamellae. We think of them as "pancakes" of diameter 600 nm, height 10 nm spaced every 50 nm. This means that there are around 40 such "pancakes" per mitochondria. The area of one of this lamellae can be thought of as the area of two discs of diameter 600 nm. The total internal area is then.

$$A_{\text{in}} = A_{\text{out}} + 2 \times 40 \times 2 \times \pi \times (0.3\ \mu\text{m})^2 \approx 50\ \mu\text{m}^2. \tag{2.52}$$

We see that $A_{\text{in}}/A_{\text{out}} \approx 7$. There is almost one order of magnitude more area in the internal membrane than in the external one!
(c) Ribosomes are located every 40 nm along the rough ER. If we assume that they are closely packed this means that the area associated with a ribosome is a disc of 40 nm in diameter with an area 1300 nm^2. This then translates into a density of ribosomes of

$$\frac{1\ \text{ribosome}}{1300\ \text{nm}^2} \approx 800\ \frac{\text{ribosomes}}{\mu\text{m}^2}. \tag{2.53}$$

(d) We model the head of a spermatozoid as a cylinder of diameter 1 μm and height 3 μm. This corresponds to a volume of $\pi \times (0.5\ \mu\text{m})^2 \times 3\ \mu\text{m} \approx 2.4\ \mu\text{m}^3$. Assuming that this is a human spermatozoid there would be 3×10^9 base pairs packaged within the sperm head. This corresponds to a packaging density of about $1.3 \times 10^9 \text{bp}/\mu\text{m}^3$.
(e) We model this lymphocyte as a flat cell of 3.7 μm in diameter. We assume that the cell has a height of 0.5 μm. Now, let's model the area covered by the cytoplasm as the outer ring of the cell. This ring has an outer diameter of 3.7 μm and an inner diameter of 2.9 μm. The area of this ring is $\pi\left[(1.85\ \mu\text{m})^2 - (1.45\ \mu\text{m})^2\right] \approx 4.1\ \mu\text{m}^2$. This corresponds to a volume available to the cytoplasm of around 2 μm^3 versus the $\pi(1.85\ \mu\text{m})^2 \times 0.5\ \mu\text{m} \approx 5.4\ \mu\text{m}^3$ corresponding to the total cell volume.

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