

## PROBLEMS\*

### 4.1 *Bad luck*

- a. You go to a casino with a dishonest coin, which you have filed down in such a way that it comes up heads 51% of the time. You find a credulous rube willing to bet \$1 on tails for 1000 consecutive throws. He merely insists in advance that if after 1000 throws you're exactly even, then he'll take your shirt. You figure that you'll win about \$20 from this sucker, but instead you lose your shirt. How could this happen? You come back every weekend with the same proposition, and indeed, usually you do win. How often on average do you lose your shirt?
- b. You release a billion protein molecules at position  $x = 0$  in the middle of a narrow capillary test tube. The molecules' diffusion constant is  $10^{-6} \text{ cm}^2 \text{ s}^{-1}$ . An electric field pulls the molecules to the right (larger  $x$ ) with a drift velocity of  $1 \mu\text{m s}^{-1}$ . Nevertheless, after 80 s you see that a few protein molecules are actually to the *left* of where you released them. How could this happen? What is the ending number density right at  $x = 0$ ? [Note: This is a one-dimensional problem, so you should express your answer in terms of the number density integrated over the cross-sectional area of the tube, a quantity with dimensions  $\mathbb{L}^{-1}$ .]
- c.  $\boxed{T_2}$  Explain why (a) and (b) are essentially, but not exactly, the same mathematical situation.

### 4.2 *Binomial distribution*

The genome of the HIV-1 virus, like any genome, is a string of "letters" (basepairs) in an "alphabet" containing only four letters. The message for HIV is rather short, just  $n \approx 10^4$  letters in all. Because any of the letters can mutate to any of the three other choices, there's a total of 30 000 possible distinct one-letter mutations.

In 1995, A. Perelson and D. Ho found that every day about  $10^{10}$  new virus particles are formed in an asymptomatic HIV patient. They further estimated that about 1% of these virus particles proceed to infect new white blood cells. It was already known that the error rate in duplicating the HIV genome was about one error for every  $3 \cdot 10^4$  "letters" copied. Thus the number of newly infected white cells receiving a copy of the viral genome with one mutation is roughly

$$10^{10} \times 0.01 \times (10^4 / (3 \cdot 10^4)) \approx 3 \cdot 10^7$$

per day. This number is much larger than the total 30 000 possible 1-letter mutations, so every possible mutation will be generated many times per day.

- a. How many distinct *two*-base mutations are there?
- b. You can work out the probability  $P_2$  that a given viral particle has *two* bases copied inaccurately from the previous generation by using the sum and product rules of probability. Let  $P = 1/(3 \cdot 10^4)$  be the probability that any given base is copied incorrectly. Then the probability of exactly two errors is  $P^2$ , times the probability

\*Problem 4.7 is adapted with permission from Benedek & Villars, 2000b.

that the remaining 9998 letters *don't* get copied inaccurately, times the number of distinct ways to choose *which* two letters get copied inaccurately. Find  $P_2$ .

- c. Find the expected number of two-letter mutant viruses infecting new white cells per day and compare to your answer to (a).
- d. Repeat (a–c) for *three* independent mutations.
- e. Suppose that an antiviral drug attacks some part of HIV but that the virus can evade the drug's effects by making one particular, single-base mutation. According to the preceding information, the virus will very quickly stumble upon the right mutation—the drug isn't effective for very long. Why do you suppose an effective HIV therapy involves a combination of *three* different antiviral drugs administered simultaneously?

### 4.3 Limitations of passive transport

Most eukaryotic cells are about  $10\ \mu\text{m}$  in diameter, but a few cells in your body are about a meter long. These are the neurons running from your spinal cord to your feet. They have a normal-sized cell body, with various bits sticking out, notably a very long axon (see Section 2.1.2 on page 43).

Many molecules needed at the tip of the axon, for example proteins, are synthesized in the cell body and packaged into vesicles or other particles. Even entire organelles, like mitochondria, need to be transported from their construction sites in the cell body to the periphery. Section 2.3.2 asserted that these objects are all transported along the axon by molecular motors. It might seem that an attractive alternative would be for them to arrive by simple diffusion, but Section 4.4.1 claimed that this mechanism is too slow. Let's see.

Model the axon as a tube 1 m long. At one end of the axon, some synthetic process creates objects similar to those seen in Figure 2.19 on page 56, maintaining them at a number density  $c_0$  (we won't need the numerical value of  $c_0$ ). Objects arriving at the axon terminal are immediately gobbled up by some other process, and so the number density at this end is zero.

- a. Use the Stokes and Einstein relations to estimate the diffusion constant  $D$  for an object the size of the vesicle in Figure 2.19b.
- b. What is the diffusive number flux  $j_{\text{diffus}}$  of these objects along the axon?
- c. In the microscope one sees organelles and other objects moving at about 400 mm per day. Convert this speed to another number flux  $j_{\text{obs}}$ , again assuming a number density of  $c_0$ .
- d. Find the ratio  $j_{\text{diffus}}/j_{\text{obs}}$  and comment.

### 4.4 Diffusion versus size

Table 4.2 lists the diffusion constants  $D$  and radii  $r$  of various biologically interesting molecules in water. Consider the last four entries. Interpret these data in light of the diffusion law. [*Hint*: Plot  $D$  versus  $1/R$ , and remember Equation 4.14.]

### 4.5 Perrin's experiment

Figure 4.17 shows some experimental data on Brownian motion taken by Jean Perrin. Perrin took colloidal particles of gutta-percha (natural rubber), with radius  $0.37\ \mu\text{m}$ . He watched their projections into the  $xy$  plane, so the two-dimensional random walk

Table 4.2: Sizes and diffusion constants of some molecules in water at 20°C.

molecule	molar mass, g/mole	radius, nm	$D \times 10^9, \text{m}^2 \text{s}^{-1}$
water	18	0.15	2.0
oxygen	32	0.2	1.0
urea	60	0.4	1.1
glucose	180	0.5	0.7
ribonuclease	13 683	1.8	0.1
$\beta$ -lactoglobulin	35 000	2.7	0.08
hemoglobin	68 000	3.1	0.07
collagen	345 000	31	0.007

[From Tanford, 1961.]

should describe their motions. Following a suggestion of his colleague P. Langevin, Perrin observed the location of a particle, waited 30 s, then observed again and plotted the net displacement in that time interval. He collected 508 data points in this way and calculated the root-mean-square displacement to be  $d = 7.84 \mu\text{m}$ . The concentric circles drawn on the figure have radii  $d/4, 2d/4, 3d/4, \dots$

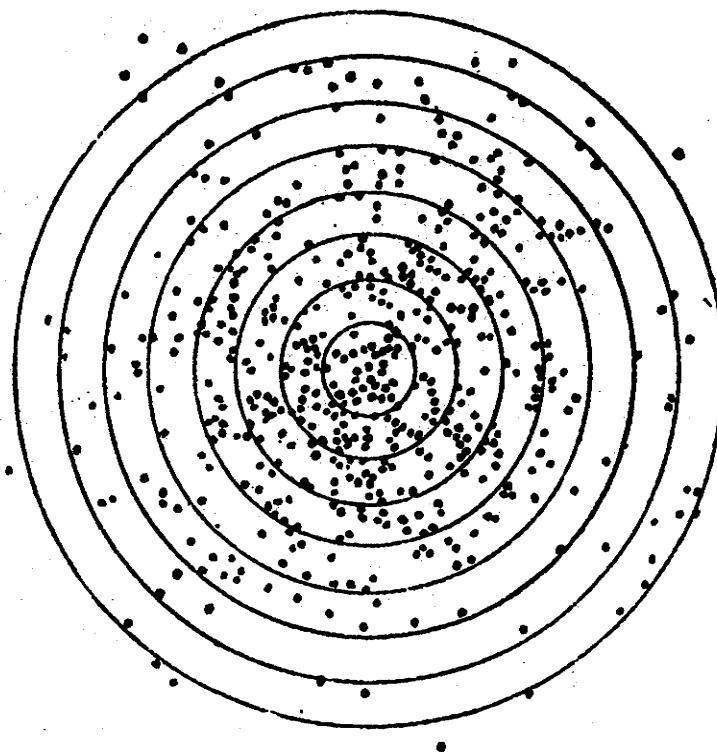


Figure 4.17: (Experimental data.) See Problem 4.5. [From Perrin, 1948.]

- Find the expected coefficient of friction for a sphere of radius  $0.37 \mu\text{m}$ , using the Stokes formula (Equation 4.14). Then work out the predicted value of  $d$ , using the Einstein relation (Equation 4.16) and compare with the measured value.

- b.  $T_2$  How many dots do you expect to find in each of the rings? How do your expectations compare with the actual numbers?

#### 4.6 Permeability versus thickness

Look at Figure 4.13 on page 137 again. Find the thickness of the bilayer membrane used in Finkelstein's experiments.

#### 4.7 Vascular design

Blood carries oxygen to your body's tissues. For this problem, you may neglect the role of the red cells: Just suppose that the oxygen is dissolved in the blood and diffuses out through the capillary wall because of a concentration difference. Model a capillary as a cylinder of length  $L$  and radius  $r$ , and describe its oxygen transport by a permeability  $\mathcal{P}$ .

- If the blood did not flow, the interior oxygen concentration would approach that of the exterior as an exponential, similarly to the concentration decay Example (page 136). Show that the corresponding time constant would be  $\tau = r/(2\mathcal{P})$ .
- But blood *does* flow. For efficient transport, the time that the flowing blood remains in the capillary should be at least  $\approx \tau$ ; otherwise the blood would carry its incoming oxygen right back out of the tissue after entering the capillary. Using this constraint, derive a formula for the maximum speed of blood flow in the capillary. Evaluate your formula numerically, using  $L \approx 0.1$  cm,  $r = 4$   $\mu\text{m}$ ,  $\mathcal{P} = 3$   $\mu\text{m s}^{-1}$ . Compare with the actual speed  $v \approx 400$   $\mu\text{m s}^{-1}$ .

#### 4.8 Spreading burst

Your Turn 4D on page 134 claimed that, in one-dimensional diffusion, an observer sitting at a fixed point sees a transient pulse of concentration pass by. Make this statement more useful, as follows: Write the explicit solution of the diffusion equation for release of a million particles from a point source in *three* dimensions. Then show that the concentration measured by an observer at fixed distance  $r$  from the initial release point peaks at a certain time.

- Find that time, in terms of  $r$  and  $D$ .
- Show that the value of concentration at that time is a constant times  $r^{-3}$  and evaluate the constant numerically.

#### 4.9 $T_2$ Rotational random walk

A particle in fluid will wander: Its center does a random walk. But the same particle will also *rotate* randomly, leading to diffusion in its orientation. Rotational diffusion affects the precision with which a microorganism can swim in a straight line. We can estimate this effect as follows.

- You look up in a book that a sphere of radius  $R$  can be twisted in a viscous fluid by applying a torque  $\tau = \zeta_r \omega$ , where  $\omega$  is the speed in radians/s and  $\zeta_r = 8\pi\eta \times$  (??) is the rotational friction coefficient. Unfortunately, the dog has chewed your copy of the book and you can't read the last factor. What is it?
- But you didn't want to know about friction—you wanted to know about diffusion. After time  $t$ , a sphere will reorient with its axis at an angle  $\theta$  to its original direction. Not surprisingly, rotational diffusion obeys  $\langle \theta^2 \rangle = 4D_r t$ , where  $D_r$  is a

rotational diffusion constant. (This formula is valid as long as  $t$  is short enough that this quantity stays small.) Find the dimensions of  $D_r$ .

- c. Use your answer to (a) to obtain a numerical value for  $D_r$ . Model the bacterium as a sphere of radius  $1 \mu\text{m}$  in water at room temperature.
- d. If this bacterium is swimming, about how long will it take to wander significantly (say,  $30^\circ$ ) off its original direction?

#### 4.10 T<sub>2</sub> Spontaneous versus driven permeation

This chapter discussed the permeability  $\mathcal{P}_s$  of a membrane to dissolved solute. But membranes also let water pass. The permeability  $\mathcal{P}_w$  of a membrane to water may be measured as follows. Heavy water, HTO, is prepared with tritium in place of one of the hydrogens; it's chemically identical to water but radioactive. We take a membrane patch of area  $A$ . Initially, one side is pure HTO, the other pure  $\text{H}_2\text{O}$ . After a short time  $dt$ , we measure some radioactivity on the other side, corresponding to a net passage of  $(2.9 \text{ mole s}^{-1} \text{m}^{-2}) \times A dt$  radioactive water molecules.

- a. Rephrase this result as a Fick-type formula for the diffusive flux of water molecules. Find the constant  $\mathcal{P}_w$  appearing in that formula. [*Hint:* Your answer will contain the number density of water molecules in liquid water, about  $55 \text{ mole/L}$ .]

Next suppose that we have ordinary water,  $\text{H}_2\text{O}$ , on both sides, but we *push* the fluid across the membrane with a pressure difference  $\Delta p$ . The pressure results in a flow of water, which we can express as a flux of volume  $j_v$  (see the general discussion of fluxes in Section 1.4.4 on page 22). The volume flux will be proportional to the mechanical driving force:  $j_v = -L_p \Delta p$ . The constant  $L_p$  is called the membrane's filtration coefficient.

- b. There should be a simple relation between  $L_p$  and  $\mathcal{P}_w$ . Guess it, remembering to check your guess with dimensional analysis. Using your guess, estimate  $L_p$ , using your answer to (a). Express your answer both in SI units and in the traditional units  $\text{cm s}^{-1} \text{atm}^{-1}$  (see Appendix A). What will be the net volume flux of water if  $\Delta p = 1 \text{ atm}$ ?
- c. Human red blood cell membranes have water permeability corresponding to the value you found in (a). Compare your result in (b) to the measured value of the filtration coefficient for this membrane,  $9.1 \cdot 10^{-6} \text{ cm s}^{-1} \text{atm}^{-1}$ .