

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 L^{-1} .]

~~α 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_{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_{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

Fig 2.19
is attached.

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	2.0
urea	60	0.4	1.1
glucose	180	0.5	0.7
ribonuclease	13 683	1.8	0.1
β -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 $d/4, 2d/4, 3d/4, \dots$

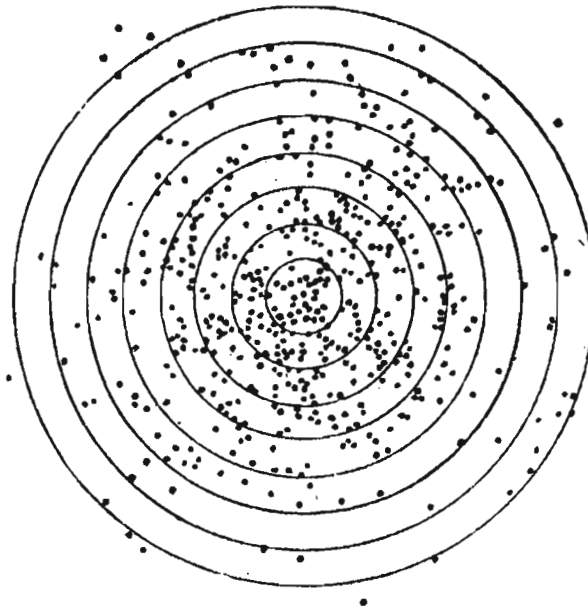


Figure 4.17: (Experimental data.) See Problem 4.5. [From Perrin, 1948.]

- 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.

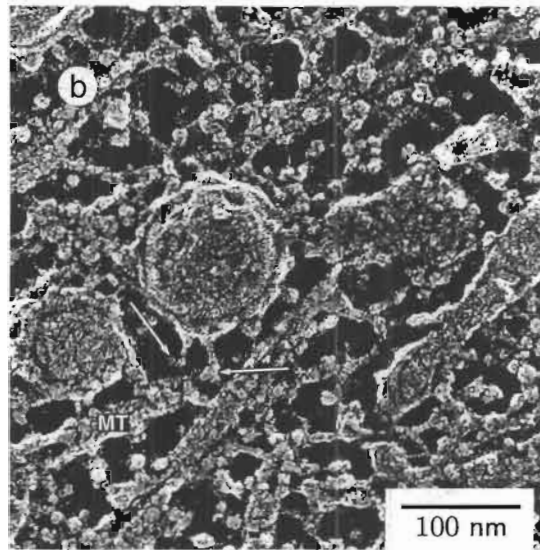
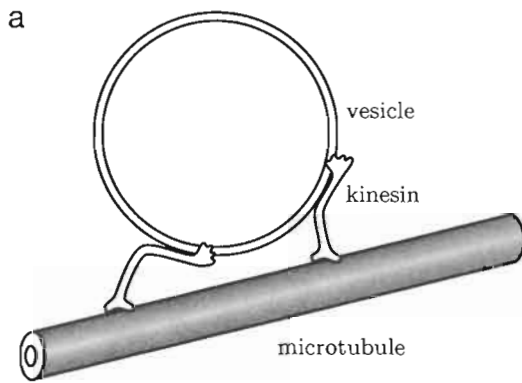


Figure 2.19: (Schematic; electron micrograph.) (a) Model showing how kinesin drags a vesicle along a microtubule. Chapter 10 will discuss the action of this single-molecule motor. (b) Micrograph appearing to show the situation sketched in (a). Arrows show the attachment points. Neurons from rat spinal cord were flash-frozen and deep-etched to create the sample. [(a) Adapted from Kandel et al., 2000. (b) Image kindly supplied by N. Hirokawa; see Hirokawa et al., 1989.]

must not rip; yet it must also be fluid enough to let the cell crawl, endocytose, and divide. We will study the remarkable properties of phospholipid molecules that reconcile these constraints in Chapter 8.

We get another surprise when we mix phospholipid molecules with water: Even without any cellular machinery, *bilayer membranes self-assemble spontaneously*. Chapter 8 will show that this phenomenon is driven by the same interactions that cause salad dressing to separate spontaneously into oil and water. Similarly, microtubules and F-actin can self-assemble from their subunits, without the intervention of any special machinery (see Figure 10.4 on page 408).

Bilayer membranes do far more than partition cells. They also carry a rich variety of molecular devices (see Figure 2.20):

- Integral membrane proteins span the membrane, projecting on both the inner and outer sides. Examples include the **channels**, which allow the passage of specified molecules under specified conditions; **receptors**, which sense exterior conditions; and **pumps**, which actively pull ions and other material across a membrane (see Figure 2.21).
- Receptors can, in turn, connect to peripheral membrane proteins, which communicate information to the interior of the cell.
- Still other integral membrane proteins anchor the cell's membrane to its underlying actin cortex, helping the cell maintain its required shape. A related example

Figure 2.20: (D) two membranes. I The surrounding embedded protein (labeled p). The f making ATP. Ch: appears at upper