The Boltzmann factor, DNA melting, and Brownian ratchets: Topics in an introductory physics sequence for biology and premedical students

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The enrollment in the new sequence was approximately 100 students. The class is evenly split between sophomores and juniors with a few seniors. The majority (80%) are biology majors, with 80% identifying themselves as premedical students, and they possess considerable biological sophistication. In many cases, they are involved in biomedical research at Yale or at the Yale School of Medicine. In many cases too, they are involved in medically-related volunteer work. The major time commitment required to do justice to a rigorous physics class has to compete with these other obligations. Therefore, an important aspect of our teaching strategy is to convince these students that physics is indeed relevant to their academic and professional goals. To engage these students, in the 2010-2011 academic year, the Yale physics department debuted a new introductory physics sequence, that, in addition to covering the basics – kinematics, force, energy, momentum, Hooke’s Law, Ohm’s Law, Maxwell’s equations etc. – also covers a number of more biologically-relevant topics, including, in particular, probability, random walks, and the Boltzmann factor. The point of view of the class is that the essential aspect of physics is that it constitutes a mathematical description of the natural world, irrespective of whether the topic is planetary motion or cellular motion.

In spite of the growing recognition that physics skills – “scholastic rigor, analytical thinking, quantitative assessment, and the analysis of complex systems” [1] – are important for biology [2] and pre-medical [1] students, these students often arrive in physics classes skeptical about the relevance of physics to their academic and professional goals. To engage these students, in the 2010-2011 academic year, the Yale physics department debuted a new introductory physics sequence, that, in addition to covering the basics – kinematics, force, energy, momentum, Hooke’s Law, Ohm’s Law, Maxwell’s equations etc. – also covers a number of more biologically-relevant topics, including, in particular, probability, random walks, and the Boltzmann factor. The point of view of the class is that the essential aspect of physics is that it constitutes a mathematical description of the natural world, irrespective of whether the topic is planetary motion or cellular motion.

The first topic is DNA melting, modelled as DNA unzipping, which provides a way to illustrate the role of the Boltzmann factor in a venue well-known to biology and pre-medical students; (2) the activity of helicase motor proteins in unzipping double-stranded DNA, for example, at the replication fork, which is an example of a Brownian ratchet; (3) force generation by actin polymerization, which is another Brownian ratchet, and for which the force and actin-concentration dependence of the velocity of actin polymerization is determined.

I. INTRODUCTION



II. THE BOLTZMANN FACTOR

"The laws of thermodynamics may easily be obtained from the principles of statistical mechanics, of which they are an incomplete expression." J.W. Gibbs [6].

Instead of introducing thermal phenomena via thermodynamics and heat engines, as might occur in a traditional introductory sequence, following the suggestion of Garcia et al. [7], we chose to assert the Boltzmann factor as the fundamental axiom of thermal physics. Building upon earlier sections of the course on probability and random walks, this approach permits us to rapidly progress to physics-based treatments of DNA melting, unzipping of double-stranded DNA at the replication fork by helicase motor proteins, and force-generation by actin-polymerization. Specifically, we assert that, for microstates i and j of a system, the probability \( p_i \) of realizing a microstate \( i \) and the probability \( p_j \) of realizing a microstate \( j \) are related via

\[
\frac{p_i}{p_j} = e^{-(\epsilon_i - \epsilon_j)/(k_B T)},
\]

where \( \epsilon_i \) is the energy of microstate \( i \), \( \epsilon_j \) is the energy...
where $\epsilon$ is the energy of the folded state.

To illustrate the Boltzmann factor in a simple example, we consider protein folding/unfolding. Protein/unfolding is an example of an isomerization reaction, in which one chemical species alternates between different molecular configurations. In this case, it is important to realize that the folded state corresponds to a single microstate, but that the unfolded state corresponds to $g$ microstates. This is because there is just one molecular configuration associated with the folded state. By contrast, the unfolded state can be viewed as a random walk in space, and therefore corresponds to $g$ different molecular configurations, one for each different random walk. If there are a total of $n$ proteins, $n_u$ of which are unfolded, and if there are $g$ possible unfolded microstates, then the probability of realizing a particular unfolded microstate ($p_u$) is equal to the probability that a protein molecule is unfolded multiplied by the probability that an unfolded protein is in the particular unfolded microstate of interest, which is one of $g$ equally-likely microstates:

$$p_u = \frac{n_u}{n} \times \frac{1}{g}. \quad (2)$$

There is a unique folded microstate, so in terms of $n$ and the number of folded proteins, $n_f$, the probability of realizing the folded microstate is simply

$$p_f = \frac{n_f}{n}. \quad (3)$$

Combining EQ. 1, EQ. 2 and EQ. 3 we find

$$\frac{n_u}{n_f} = g e^{-(\epsilon_u - \epsilon_f)/(k_B T)}, \quad (4)$$

where $\epsilon_u$ is the energy of any of the unfolded states and $\epsilon_f$ is the energy of the folded state.

### III. DNA MELTING

#### A. DNA unzipping/zipping as a chemical reaction

Next, we examine DNA melting, according to the model of Ref. 3 in which DNA melting is equivalent to DNA unzipping. We treat DNA zipping and unzipping as a set of isomerization reactions. To this end, we consider a population of identical DNA strands each of which contains a junction between dsDNA and ssDNA. Fig. 1 illustrates the reactions involving the DNA strand with $i$ paired base pairs. This is the chemical species in the center. The species on the left and right are DNA strands with $i + 1$ and $i - 1$ paired base pairs, respectively. The relevant reaction rates are $\alpha$, which is the zipping rate, and $\beta$, which is the unzipping rate. When $\alpha > \beta$, the DNA zips up. When $\alpha < \beta$, the DNA unzips. As suggested in Fig. 1, $n_i$ is the mean number of DNA strands with $i$ paired base pairs, etc.

We have previously discussed in class that how the concentration of chemical species changes in time can be described by chemical rate equations. With the help of Fig. 1 we are thus lead to an equation for the rate of change of $n_i$ in terms of $\alpha, \beta, n_i, n_{i-1}$, and $n_{i+1}$:

$$\frac{dn_i}{dt} = -\alpha n_i - \beta n_i + \alpha n_{i-1} + \beta n_{i+1}. \quad (5)$$

At equilibrium, at a temperature $T$, on-average nothing changes as a function of time, so $dn_i/dt = 0$. Thus,

$$0 = -\alpha - \beta + \alpha \frac{n_{i-1}}{n_i} + \beta \frac{n_{i+1}}{n_i}. \quad (6)$$

The factor $n_{i-1}/n_i$, which is the ratio of the mean number of DNA strands with $i - 1$ zipped base pairs to the mean number with $i$ zipped base pairs, is equal to the ratio of the probability that a particular DNA strand has $i - 1$ zipped base pairs to the probability that it has $i$ zipped base pairs. Thus, this factor is given by a Boltzmann factor (cf. EQ. 4):

$$\frac{n_{i-1}}{n_i} = g e^{-\epsilon/(k_B T)} = e^{-(\epsilon - k_B T \ln g)/(k_B T)} = e^{-\Delta G/(k_B T)}, \quad (7)$$

where $\epsilon$ is the energy required to unzip one additional base pair (so $\epsilon$ is positive) and $g$ specifies that the two unzipped ssDNA bases have a factor $g$ times as many microstates as the single dsDNA base pair they replace. The last equality in EQ. 7 defines the free energy required.
It follows from EQ. 10 that
\[ \Delta G = \epsilon - k_B T \ln g. \] (8)

Students are familiar with \( \Delta G \) from their chemistry classes. Similarly, we have
\[ \frac{n_{i+1}}{n_i} = e^{\Delta G/(k_B T)}. \] (9)

Substituting EQ. 7 and EQ. 9 into EQ. 6, we have
\[ 0 = -\alpha - \beta + \alpha e^{-\Delta G/(k_B T)} + \beta e^{\Delta G/(k_B T)}. \] (10)

It follows from EQ. 10 that
\[ \frac{\beta}{\alpha} = e^{-\Delta G/(k_B T)}. \] (11)

EQ. 11 informs us that the DNA unzips, i.e. \( \beta > \alpha \), only if \( \Delta G < 0 \), i.e. only if \( \epsilon < k_B T \ln g < 0 \). In order for this condition \( \epsilon < k_B T \ln g < 0 \) to be satisfied, it is necessary that \( T > \epsilon/(k_B \ln g) \). If we define the DNA “melting temperature” to be \( T_M = \epsilon/(k_B \ln g) \), we see that the DNA unzips for \( T > T_M \), while it zips up for \( T < T_M \).

This phenomenon is an essential ingredient in DNA multiplication by polymerase chain reaction (PCR), which is well-known to the students, and for which Kary Mullis won the 1993 Nobel Prize in Chemistry. The first step in PCR is to raise the temperature above \( T_M \), so that each dsDNA strand unzips to become two ssDNA strands. When the temperature is subsequently reduced in the presence of oligonucleotide primers, nucleotides and DNA polymerase, each previously-unzipped, ssDNA strand templates its own conversion to dsDNA. This doubles the original number of dsDNA strands because a new dsDNA strand is created for each ssDNA. PCR involves repeating this temperature cycling process multiple (\( N \)) times, with the result that the initial number of dsDNA molecules is multiplied by a factor of \( 2^N \). Thus, initially tiny quantities of dsDNA can be hugely amplified, and subsequently sequenced.

**B. DNA unzipping/zipping from a random-walk point of view**

It is also instructive to view DNA zipping/unzipping as a biased random walk, which students have previously studied in the class. In this context, if we consider a dsDNA-ssDNA junction, the probability of zipping up one base pair in a time \( \Delta t \) is \( \alpha \Delta t \), and the probability of unzipping one base pair in a time \( \Delta t \) is \( \beta \Delta t \). For small enough \( \Delta t \) it is reasonable to assume that the only three possibilities are (1) to zip up one base pair or (2) to unzip one base pair or (3) to do nothing. Therefore, since probabilities sum to unity, we must have that the probability to do nothing is \( 1 - \alpha \Delta t - \beta \Delta t \). Given these probabilities, and the length of a base pair, \( b \), we may readily calculate the mean displacement of the ssDNA-dsDNA junction in a time \( \Delta t \):
\[ \Delta x_j = b(\beta - \alpha)\Delta t, \] (12)

where zipping corresponds to a negative displacement of the ss-to-ds junction. Since the mean of the sum of \( n \) identically-distributed, statistically-independent random variables is \( n \) times the mean of one of them (which students learned earlier in the course), then in a time \( t = n \Delta t \) the mean displacement of the ssDNA-dsDNA junction is
\[ x_j = n \Delta x_j = \frac{t}{\Delta t} \Delta x_j = \frac{t}{\Delta t} b(\beta - \alpha) \Delta t = b(\beta - \alpha) t. \] (13)

The corresponding drift velocity of the ssDNA-dsDNA junction is
\[ v_j = b(\beta - \alpha) = b\alpha(e^{-\Delta G/(k_B T)} - 1) \] (14)

This is the drift velocity of a dsDNA-ssDNA junction in terms of the zipping up rate (\( \alpha \)) and the unzipping rate (\( \beta \)), or the zipping rate (\( \alpha \)) and the unzipping free energy (\( \Delta G \)). We will come back to this result below, but we note now that EQ. 14 is appropriate only when the junction is far from a helicase.

As defined in EQ. 8 \( \Delta G \) is the change in free energy that occurs when one additional base pair is unzipped. Thus, as far as this expression for \( \Delta G \) is concerned, the final, “product” state is the unzipped state, and the initial, “reactant” state is the zipped state. Thus, unzipping corresponds to the forward direction of the reaction. We may make contact with what students have learned in chemistry classes, namely that a reaction proceeds forward if \( \Delta G \) is negative, by pointing out that EQ. 14 informs us that the unzipping reaction proceeds forwards (i.e. that \( v_j > 0 \)) only for \( \Delta G < 0 \), exactly as we are told in chemistry classes. Here, though, this result is derived from a more basic principle, namely the Boltzmann factor.

**IV. HELICASE DNA-UNZIPPING ACTIVITY**

**A. Helicases**

Helicases are a class of motor proteins (a.k.a. molecular motors), which perform myriad tasks in the cell by catalyzing ATP-to-ADP hydrolysis and using the free energy released in this reaction to do work. The importance of helicases may be judged from the fact that 4% of the yeast genome codes for some kind of helicase. One of their roles is to unzip dsDNA and/or dsRNA. Thus, helicases play an indispensable role in DNA replication, for example. To engage students in this topic, we start by showing a number of online movies illustrating the DNA-unzipping activity of helicase motor proteins at the replication fork. These movies also present
an opportunity for active learning in which we ask students to discuss with their neighbors what is misleading about the videos. The essential point is that, wonderful as they are, the videos suggest that everything proceeds deterministically. By contrast, as we will discuss, all of the processes depicted are actually random walks, but with a drift velocity that corresponds to their progress. We also point out that, on the medical side, Werner syndrome, which involves accelerated aging, is caused by a mutation in the *WRN* gene which codes for the helicase WRN [13].

### B. Brownian ratchet mechanism of helicase activity

One proposed mechanism for how helicase unzips DNA is as follows. The helicase steps unimpeded on ssDNA towards a ss-to-ds junction, until it encounters the junction, which then blocks its further progress, because the helicase translocates only on ssDNA. However, at the junction, there is a non-zero probability per unit time for the junction to thermally unzip one base pair, because of the Boltzmann factor. It is then possible for the helicase to step into the just-unzipped position. If the helicase does this, the DNA is prevented from subsequently zipping back up again. In this way, the junction is unzipped one step. Repeating this process many times leads to the complete unzipping of the DNA. Because this mechanism relies on random Brownian motions to both unzip the DNA and to move the helicase into the just-unzipped position, the helicase is said to be a Brownian ratchet [5], analogous to Feynman’s thermal ratchet [14].

### C. Helicase translocation from a random-walk point of view

Just as the motion of the ss-to-ds junction may be conceived as a random walk, so may be the translocation of the helicase on ssDNA. In this case, the probability of the helicase stepping one base pair towards the junction (+b) in a time $\Delta t$ is $k_+ \Delta t$, and the probability stepping one base pair away from the junction ($-b$) in a time $\Delta t$ is $k_- \Delta t$, where $k_+$ and $k_-$ are the rate of stepping towards the junction and the rate of stepping away from the junction, respectively. Since probabilities sum to unity, and we assume that the only three possibilities in a small time $\Delta t$ are to step towards the junction one base pair or to step away from the junction one base pair or to not do anything, we must have that the probability to do nothing is $1 - k_+ \Delta t - k_- \Delta t$. Given these probabilities, and the length of a base pair, $b$, we may calculate the mean displacement of the helicase in a time $\Delta t$:

$$\Delta x_h = b(k_+ - k_-)\Delta t.$$  

(15)

Since the mean of the sum of $n$ identically-distributed, statistically-independent random variables is $n$ times the mean of one of them, then in a time $t = n\Delta t$ the mean displacement of the helicase is

$$x_h = n\Delta x_h = \frac{t}{\Delta t}b(k_+ - k_-)\Delta t = b(k_+ - k_-)t.$$  

(16)

The corresponding drift velocity of the helicase is

$$v_h = b(k_+ - k_-).$$  

(17)

This is the drift velocity of a helicase in terms of the stepping-towards-the-junction rate ($k_+$) and the stepping-away-from-the-junction rate ($k_-).$ Just like EQ. [14] EQ. [17] is appropriate only when the helicase is far from the junction.

An important additional point, concerning helicase translocation on ssDNA, is that, as we saw in EQ. [11] the ratio of forward and backward rates is given by a change in free energy. Thus, for helicase stepping we must expect, in analogy with EQ. [11] that the ratio of stepping rates is given by

$$\frac{k_+}{k_-} = e^{\Delta G'/(k_BT)},$$  

(18)

where $\Delta G'$ is a free energy change. But what free energy change? The answer can be gleaned from the observation that helicases, and motor proteins generally, can be thought of as enzymes, which catalyze ATP-to-ADP hydrolysis, which is coupled to the helicase’s translocation. It follows that $\Delta G'$ in EQ. [18] corresponds to the free energy difference between ATP and ADP. (Note that $\Delta G'$, as specified in EQ. [18] must be positive, in order to ensure that $k_+ > k_-$ so that the helicase translocates on ssDNA preferentially towards the ssDNA-to-dsDNA junction.)
D. Clash of the titans

So far, we have considered the situation when the ds-to-ss junction and the helicase are far apart. To determine how helicase unzips dsDNA, it is necessary to determine what happens when these two objects come into close proximity, given that they cannot cross each other. To elucidate what happens in this case, we show to the class a simple Mathematica Demonstration that simulates these two non-crossing random walks [15]. The simulation treats both the location of the helicase and the location of the ds-to-ss junction as random walks. At each time step within the simulation, the helicase ordinarily steps in the positive $x$-direction, towards the junction, with probability $k_+ \Delta t$ and in the negative $x$-direction, away from the junction, with probability $k_- \Delta t$, while the junction ordinarily steps in the positive $x$-direction, zipping up one step, with probability $\alpha \Delta t$ and in the negative $x$-direction, unzipping one step, with probability $\beta \Delta t$. However, in the simulation, if the helicase and the junction are neighbors, neither one is permitted to step to where it would overlap with the other. Thus, the helicase and the junction cannot cross. An example of the simulational results is shown in Fig. 3 where the orange trace represents helicase location as a function of time and the green trace represents the location of the ssDNA-to-dsDNA junction as a function of time. Evidently, the helicase and the junction track together, therefore, we reason that EQ. 12 should be modified to read

$$\Delta x_j = b(\beta - \alpha P) \Delta t.$$ (19)

Similarly, EQ. 15 should be modified to read

$$\Delta x_h = b(k_+ P - k_-) \Delta t.$$ (20)

It follows that the drift velocities are modified to read

$$v_j = b(\beta - \alpha P),$$ (21)

and

$$v_h = b(k_+ P - k_-).$$ (22)

However, from the simulation, it is also clear that, while the helicase is unzipping DNA, the helicase and the junction must have the same drift velocity $i.e.$

$$v_h = v_j$$ (23)

or

$$b(k_+ P - k_-) = b(\beta - \alpha P).$$ (24)

We can solve this equation to determine $P$:

$$P = \frac{k_- + \beta}{k_+ + \alpha}.$$ (25)

Furthermore, we can use this expression for $P$ to determine the drift velocity at which the helicase unzips the dsDNA by substituting into EQ. 22 Setting $v_j = v_h = v$, we find

$$v = b \left( \frac{\beta}{\alpha} - \frac{k_-}{k_+} \right).$$ (26)

EQ. 26 represents the velocity at which helicase unzips dsDNA according to the Brownian ratchet mechanism. The numerator in EQ. 26 is the difference of two rate ratios. It follows, using EQ. 11 and EQ. 18 in EQ. 26 that

$$v = b \left( \frac{e^{-\Delta G/(kbT)} - e^{-\Delta G'/(kbT)}}{\frac{1}{k_+} + \frac{1}{\alpha}} \right).$$ (27)

EQ. 27 informs us that whether or not helicase unzips dsDNA depends solely on whether $\Delta G' > \Delta G$ or
not. For $\Delta G' > \Delta G$, the drift velocity of the helicase-plus-junction is positive, corresponding to the helicase unzipping the dsDNA. In fact, for one base pair, we have $\Delta G \approx 3k_BT$, while for the hydrolysis of one ATP molecule, we have $\Delta G' \approx 16k_BT$, so indeed the helicase has plenty of free energy to do its work. In fact, energetically, one ATP hydrolysis cycle could unzip up to about 5 base pairs.

In fact, beautiful, single-helicase experiments [16] suggest that the simple Brownian ratchet mechanism of helicase DNA-unzipping activity, presented here, should be refined by incorporating both a softer repulsive potential between the helicase and the ds-to-ss junction than the hard-wall potential implicit in our discussion, and suitable free energy barriers between different microstates of the helicase and junction [4, 10, 16]. Appropriate choices of the potential and the barriers permit the helicase to unzip dsDNA faster than would occur in the case of a hard-wall potential. A force $(f)$, that tends to unzip the DNA, can be incorporated by replacing $\alpha$ with $\alpha e^{-fb/(k_BT)}$ and $\beta$ with $\beta e^{fb/(k_BT)}$.

V. FORCE GENERATION BY ACTIN POLYMERIZATION

A. Actin polymerization is a Brownian ratchet

The mechanism by which actin or tubulin polymerization exerts a force also a Brownian ratchet [5, 17, 18] and is schematically illustrated in Fig. 4. In the case of a load, $f$, applied to a cell membrane, the cell membrane is in turn pushed against the tip of an actin filament, which usually prevents the addition of an additional actin monomer (G-actin) of length $a$ to the tip of the actin filament (F-actin). However, with probability specified by a Boltzmann factor, the membrane’s position relative to the tip, $z$, occasionally fluctuates far enough away from the filament tip ($z > a$) to allow a monomer to fit into the gap. If a monomer does indeed insert and add to the end of the filament, the result is that the filament and therefore the membrane move one step forward, doing work against the load force. Repeating this many times for many such filaments gives rise to cell motility against viscous forces. In class we also show movies showing cells moving as a result of actin polymerization [19], and Listeria monocytogenes actin “rockets” [20].

B. Actin polymerization as a biased random walk

Similarly to EQ. 12 and EQ. 15 we can write down an expression for the mean displacement of the filament tip in a time $\Delta t$ in the absence of a nearby membrane:

$$\Delta x = a(c k_+ - k_-) \Delta t$$  \hspace{1cm} (28)

where $c$ is the concentration of G-actin, $a$ is the length of an actin monomer, $k_+$ is the actin on-rate, and $k_-$ is the actin off-rate. However, if the membrane is nearby, it is only possible to add an actin monomer if the distance between the filament and the membrane is greater than $a$. Assuming that the time-scale for membrane fluctuations is much faster than that for adding actin monomers, if the probability, that the membrane-filament tip distance is greater than $a$, is $P$, then EQ. (28) is modified to read

$$\Delta x = a(c k_+ P - k_-) \Delta t,$$ \hspace{1cm} (29)

and the drift velocity of the tip is

$$v = a(c k_+ P - k_-).$$ \hspace{1cm} (30)

But application of the Boltzmann factor informs us that, when the force on the membrane is $f$, the probability that the gap is greater than $a$ is

$$P = e^{-fa/(k_BT)},$$ \hspace{1cm} (31)

so that

$$v = a(c k_+ e^{-fa/(k_BT)} - k_-).$$ \hspace{1cm} (32)

This is the force-velocity relationship for an actin [18] or tubulin [17] filament. Although the load, $f$, is applied...
to the membrane, the velocity is constant. Therefore, according to Newton's third Law, as the students know, there can be no net force on the membrane. We may deduce that the load is balanced by an equal and opposite force, generated by the polymerization ratchet.

VI. CONCLUSIONS

Three, interrelated biologically-relevant examples of biased random walks were presented. First, we presented a model for DNA melting, modelled as DNA unzipping, which provides a way to illustrate the role of the Boltzmann factor in a venue well-known to the students. Second, we discussed the activity of helicase motor proteins in unzipping double-stranded DNA, for example, at the replication fork, which is an example of a Brownian ratchet. Finally, we treated force generation by actin polymerization, which is another Brownian ratchet, and for which we can determine how the velocity of actin polymerization depends on actin concentration and on load. In each of these examples, building on an earlier coverage of biased random walks, biology and pre-medical students in an introductory physics sequence at Yale were lead to the realization that a physics-based approach permits a deeper understanding of a familiar biological phenomenon.

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