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John F. Beausang
University of Pennsylvania

Chiara Zurla
Emory University

Laura Finzi
Emory University

Luke Sullivan
Ursinus College

Philip C. Nelson
University of Pennsylvania, nelson@physics.upenn.edu

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Abstract

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Disciplines

Physical Sciences and Mathematics | Physics

Comments

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Elementary simulation of tethered Brownian motion

John F. Beausang

Department of Physics and Astronomy, University of Pennsylvania, Philadelphia, Pennsylvania 19104

Chiara Zurla and Laura Finzi

Department of Physics, Emory University, Atlanta, Georgia 30322

Luke Sullivan

Ursinus College, Collegeville, Pennsylvania 19426-1000

Philip C. Nelson^{a)}

Department of Physics and Astronomy, University of Pennsylvania, Philadelphia, Pennsylvania 19104

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We describe a simple simulation, suitable for an undergraduate project or graduate problem set, of the Brownian motion of a particle in a Hooke's law potential well. Understanding this physical situation is necessary in many experimental contexts, for instance in single molecule biophysics, and its simulation helps students appreciate the dynamical character of thermal equilibrium. The simulation captures behavior seen in experimental data on tethered particle motion. © 2007 American Association of Physics Teachers.

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I. INTRODUCTION

Introductory courses in statistical physics often place their greatest emphasis on average quantities measured in thermodynamic equilibrium. The study of equilibrium gives many powerful results without needing to delve into the dynamics. This simplicity stems in part from the fact that for thermodynamic equilibrium, we are not interested in the time dependence (dynamics). Thus, concepts such as friction and viscosity are not typically discussed.

However, there are compelling reasons to introduce students to the dynamical aspects of thermal systems as early as possible—perhaps even before embarking on a detailed study of equilibrium.^{1,2} One reason is that students can easily miss the crucial steps needed to go from a basic appreciation that “heat is motion” to understanding the Boltzmann distribution, and thus can end up with a blind spot in their understanding of the foundations of the subject. Although any kind of rigorous proof of this connection is out of place in a first course, a demonstration of how it works in a sample calculation can cement the connection.

A second reason to give more attention to dynamical phenomena is the current increase in student interest in biological physics. Much current experimental work is on the molecular processes of life or their analogs at the single molecule level, where simple mathematical descriptions capture the observed behavior.

One familiar setting where simple models describe the dynamics well is the random walk and its relation to diffusion. Reference 2 shows an attempt to present classical statistical mechanics starting from the random walk, building on earlier texts such as Ref. 1. The link between thermal motion and the Boltzmann distribution emerges naturally in the analysis of sedimentation equilibrium, where we require that in equilibrium, diffusive changes in a concentration distribution must cancel changes caused by drift from a constant external force field (gravity).

In this article we discuss another generalization of free Brownian motion that is important for interpreting a large class of current experiments in single molecule biophysics: the Brownian motion of a micrometer-size particle attached

to a linear spring. Typically the particle is a spherical bead, and the spring is the effect of either an optical trap or a polymer tethering the bead to a fixed point. We investigate the dynamics of fluctuations of such a particle in equilibrium; that is, the equilibrium thermal motion of an overdamped harmonic oscillator. Although the analytic solution of this system appears in some undergraduate textbooks, the derivation is complex (see, for example, Ref. 3). However, we have found that the simulation of the system is a good project for undergraduates familiar with, for example, Ref. 1. Such a simulation brings insight into the emergence of equilibrium behavior from independent random steps and also can serve as an entry into the topic of equilibrium fluctuations.

Section II gives some background on the two types of experiments that we wish to model. Section III sets out the framework of the calculation. In essence, we create a simulated time series for the motion of a tethered bead by constructing a series of small time steps. At each step, the bead's displacement is the vector sum of a random component, which by itself would give rise to ordinary Brownian motion, plus a deterministic component. The latter motion reflects the drift of the bead in its viscous environment, under the influence of a spring that pulls it toward the attachment point. Section IV shows that this simple model yields a fairly good account of some experimental data. An implementation of the simulation written in MATLAB is available from EPAPS.⁴

II. EXPERIMENTAL BACKGROUND

As motivation, we briefly mention two contexts in which Brownian motion in a harmonic (Hooke's law) trap has played a role in recent biological physics experiments.

Optical trapping^{2,5} is now an everyday tool for the manipulation of micrometer-scale objects (typically a polystyrene bead), and indirectly of nanometer-scale objects attached to them (typically DNA, RNA, or a protein). In this method, a tightly focused laser spot creates a restoring force that pushes a bead toward a particular point in space. When the trapping beam has a Gaussian profile, the resulting force on the bead is approximately linear in the bead displacement

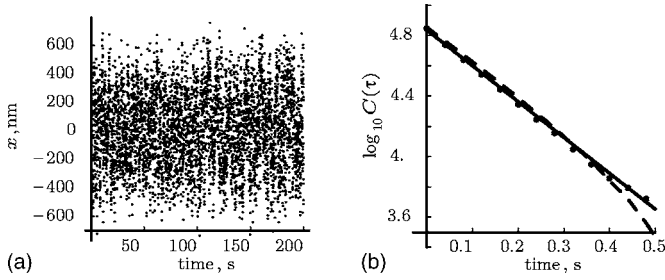


Fig. 1. (a) Sample data for the x -component of the motion of a bead of radius $R_{\text{bead}} \approx 240$ nm, attached to a DNA tether of length $L_{\text{tether}} \approx 3500$ basepairs or ≈ 1200 nm. The experiment and the protocols used to remove drift from the raw data are described in Ref. 7. For clarity only the first 200 s of data are shown; the full run lasted 600 s. (b) Logarithm of the autocorrelation function of x expressed in nm^2 (see text). Dots, experimental data. Dashed line, simulation described in this paper, using the parameters $A_{\text{eff}}=72$ nm and effective viscosity 2.4 times that of water in bulk. The solid line is the analytic solution, using the same parameters as in the simulation.

to a good approximation. Thus the bead executes Brownian motion in a harmonic potential well. In such a well the motions along the three principal axes of the well are independent.

The bead's motion in one or two dimensions can be tracked to high precision, for example by using interferometry, thus yielding a time series. The probability distribution of the observed bead locations reflects a compromise between the restoring force, pushing the bead to the origin, and thermal motion, which randomizes its location. The outcome of this compromise is a Gaussian distribution of positions, from which we can read the strength of the harmonic restoring force (the "trap stiffness"). For practical reasons it is often more accurate to obtain the trap stiffness and the bead's effective friction constant from the autocorrelation function of the bead position (see Sec. IV). For example, slow microscope drift can spoil the observed probability distribution function.⁵

Our second example concerns tethered particle motion.⁶ In this technique a bead is physically attached to a tether consisting of a single strand of DNA. The other end of the tether is anchored to a microscope slide and the resulting bead motion is observed. Changes in the bead's motion reflect conformational changes in the tether, for example, the binding of proteins to the DNA or the formation of a long-lived looped state. Figure 1(a) shows data for a situation where such conformational changes are absent, that is, simple tethered particle motion.

As in the optical trap case, we can discard the dynamical information in the time series by making a histogram of the particle locations. Figure 2(a) shows the frequencies of occurrence of various values of x . Detailed agreement between theory and experiment has been obtained for these histograms, including the slight deviation from Gaussian distribution shown in Fig. 2(a).^{7,8} Here we are interested in a less sophisticated treatment of a more general question: Can we understand at least some aspects of the *dynamical* information contained in data like those in Fig. 1?

Figure 1(b) shows the logarithm of the autocorrelation function, $C(\tau) \equiv \langle x(t+\tau)x(t) \rangle$, where the brackets denote the average over t . At $\tau=0$ this quantity is the mean square displacement, which would diverge for a free particle but instead has a finite value determined by the equipartition theorem. At large times the autocorrelation function goes to zero,

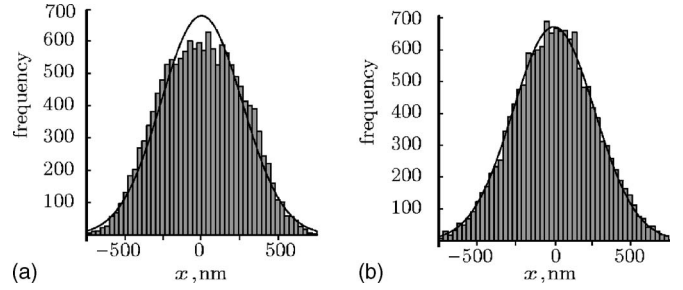


Fig. 2. (a) Histogram of measured bead position x for the experimental data shown in Fig. 1. The solid curve shows a Gaussian distribution with the same normalization and variance. (b) Similar histogram from the simulation. The solid curve shows the result of the analytic solution, using the same parameters as used for the simulation.

because two independent measurements of x are as likely to lie on opposite sides of the tethering point as they are to lie on the same side. The autocorrelation function should fall exponentially with τ , as it does in Fig. 1(b).³

III. SIMULATION BACKGROUND

We wish to simulate the motion of a bead of radius R_{bead} attached to a tether of length L_{tot} and compare our results to experimental data. To do so we need to know a specific property of DNA in typical solution, namely its persistence length $A \approx 45$ nm.²

We assume that the external forces acting on the bead are a hard wall repulsion from the microscope slide, a tension force from the tether, and random collisions with surrounding water molecules (see Sec. V for a further discussion). The tension force produces an effective potential well that keeps the bead close to its attachment point. At low relative extension, the tension exerted by a semiflexible polymer such as DNA is approximately given² by $f = -\kappa x$. The effective spring constant is $\kappa = 3k_B T / (2AL_{\text{tot}})$, where $k_B T \approx 4.1 \times 10^{-21}$ J is the thermal energy at room temperature and L_{tot} is the contour length of the polymer (DNA). The temperature dependence of κ reflects the entropic character of polymer elasticity; it is this dependence that makes a stretched rubber band retract more strongly when heated.² Note that the persistence length A enters our problem here, setting the overall scale of the spring constant κ .

The motion in each of the x , y , and z directions is independent. Because the microscopy observes only the x and y motions, we can reduce the problem to a two-dimensional one and forget about the hard-wall force, which acts only along the z direction. We can simplify the problem still further by examining only the x coordinate of the bead position.

There is a subtlety in that we do not directly observe the endpoint of the polymer (DNA) in an experiment. Rather, we observe the image of the bead; the image analysis software reports the location of the bead center, a distance R_{bead} from the attachment point. Thus the time series in Fig. 1(a) reflects the motion of the endpoint of a composite object, a semiflexible polymer (DNA) attached by a flexible link to a stiff segment of length R_{bead} . To deal simply with this complication, we note that a semiflexible polymer (like DNA) can also be approximately regarded, for the purpose of finding its force-extension relation, as a chain of stiff segments of length $2A$. In our case $2A \approx 100$ nm is not much larger than R_{bead} . Thus, we approximate the system as a single polymer

chain with effective length $L_{\text{tot}}=L_{\text{tether}}+R_{\text{bead}}$ and an effective persistence length A_{eff} somewhat larger than A . In the data we present, $L_{\text{tether}}\approx 3500$ basepairs or ≈ 1200 nm. We will fit the data to obtain A_{eff} .

To model the bead's motion, we note that it falls well within the low Reynolds number regime, where inertial effects are negligible.^{1,2,9} To confirm this assertion, we make an estimate based on the observed fluctuations of the bead position, which is $\approx \pm 500$ nm. Suppose we release a bead at this distance from the center. The spring force then moves the bead toward the center at speed $v=-\kappa x/\zeta$, where ζ is the bead's friction constant in water. The Stokes relation gives $\zeta=6\pi\eta R_{\text{bead}}$, where $\eta\approx 10^{-3}$ Pa s is the viscosity of water.^{1,2} We substitute the Stokes relation into the relation for the Reynolds number $\mathcal{R}=vR_{\text{bead}}\rho_{\text{m}}/\eta$, where ρ_{m} is the mass density of water, and find $\mathcal{R}\approx 10^{-6}$, which is small.

Consider the bead's position at times separated by intervals Δt . Without the tether, the bead would take independent random steps, each displacement drawn from a Gaussian distribution with mean-square step length $2D(\Delta t)$, where D is the bead's diffusion constant. The friction constant ζ is related to D by the Einstein relation,^{1,2} $\zeta=k_{\text{B}}T/D$. If the bead were subjected to a constant force f (for example, gravity), we could get its net motion by superimposing an additional deterministic drift on the random steps of^{1,2} $\Delta_{\text{drift}}x=(f/\zeta)\Delta t$. For the tethered case we instead use a position-dependent force $-\kappa x$ at each step, where x is the current displacement. For small enough Δt (perhaps smaller than the actual video frame rate), x will be roughly constant during the step, justifying this substitution.

IV. SIMULATION RESULTS

The simulation implements a Markov process. That is, we divide time into steps Δt that are smaller than the observation rate, but much longer than the randomizing collision time of water molecules with the bead; then to a good approximation each step is independent of prior steps, depending only on the bead's position at the start of the step. We take each step to be the sum of a random, diffusive component, drawn from a Gaussian distribution with mean square displacement $2D(\Delta t)$, and a drift component $-D\kappa x\Delta t/k_{\text{B}}T$. We choose the value of Δt small enough so that each step is much smaller than the overall bead excursion (a few hundred nm). The constants $D=k_{\text{B}}T/(6\pi\eta_{\text{eff}}R_{\text{bead}})$ and $\kappa=3k_{\text{B}}T/(2A_{\text{eff}}L_{\text{tot}})$ contain two unknown fit parameters, the effective persistence length A_{eff} and the viscosity η_{eff} . The output of the simulation is the probability distribution of the positions, and the autocorrelation function, which we compare to experimental data.

The simulation is considered to be successful if the two fit parameters take values reasonably close to the expected values, differing in the expected directions, and the full functional forms of the output agree with experimental data. Figures 1(b) and 2 show that the simple model works well. Our simulation took $\Delta t=0.625$ ms, for a total of about a million steps, which were sampled every 40 ms for comparison to the experimental data. The best fit values of the parameters, $A_{\text{eff}}=72$ nm and η_{eff} equal to 2.4 times that of water in bulk, are both somewhat greater than their standard values, as expected.

As mentioned in Sec. I, analytic equations exist for the quantities we calculated.³ These formulas are shown as solid curves in Figs. 1(b) and 2(b).

V. DISCUSSION

Our model made some naive simplifications. Two that have been mentioned involve the role of the bead radius and the sources of drag on the bead. In addition, there is a time scale for rearrangements of the DNA needed to change its extension, and for rotatory diffusion of the bead, which changes the location of the attachment point relative to its center. All of these effects have been assumed to be lumped into effective values of the fit parameters.

Despite these simplifications, we obtained two key qualitative aspects of the experimental data as outputs from the model. The simulated autocorrelation function of the equilibrium fluctuations has the expected, and experimentally observed, exponential form. Moreover, the simulated histogram of bead positions has the Gaussian form we would expect for motion in a linear potential well, again roughly in accord with the data. Both of these results emerge as statistical properties of a large number of simple steps, each involving only a diffusive step combined with a drift step based on the current bead location.

The insights obtained from this simulation are different from those obtained from the analytical solution. Students can see the average behavior emerging from the random noise as the simulation size grows, for example the emergence of the Boltzmann distribution from individual steps that do not contain it in any obvious way. Students can also see how, despite the near independence of each step from all previous steps, the resulting trajectories have long-time correlations, and how the experimental measurement of those correlations permits the determination of system parameters. In addition, the simulation approach opens the door to replacing the assumption of a harmonic potential by other functional forms. For example, students will note that the experimental distribution of x values is not quite Gaussian (Fig. 2), in part because the entropic elasticity of a semiflexible chain (such as DNA) does not quite follow Hooke's law appropriate for a flexible chain. Students can readily modify the force law (which enters the deterministic drift step) to obtain better agreement with the data.

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^aElectronic mail: nelson@physics.upenn.edu

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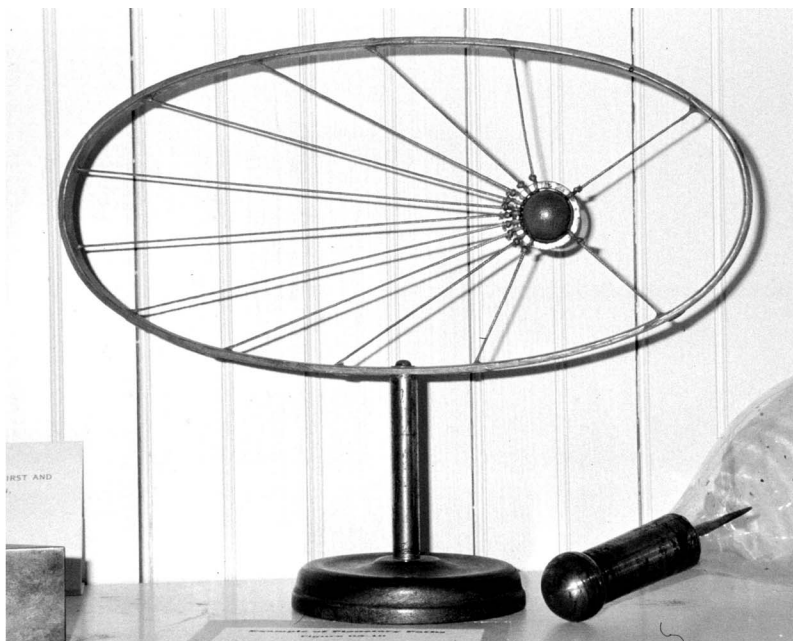
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¹²Note that the presence of the nearby wall creates additional hydrodynamic drag on the bead, not accounted for by the Stokes formula (see Refs. 10 and 11). Moreover, the tether itself incurs significant hydrodynamic drag impeding the system's motion. For simplicity, we acknowledge these complications by fitting to obtain an effective viscosity η_{eff} , which we expect to be larger than the value appropriate to water in bulk.



Kepler's Laws Demonstrator. In modern terms, the three laws developed by Johann Kepler (1571–1630) to describe planetary motion around the sun are: 1. The planets move in ellipses with the sun at the shared focus; 2. The line joining the sun and a planet sweeps out equal areas in equal times; and 3. The square of the time of revolution of each planet is proportional to the cube of its mean distance from the sun. This model from Transylvania University shows the form of the elliptical orbit. I spent some time comparing the areas swept out in what I think were intended to be equal times, and they are certainly *not* equal. I suspect that it is from the second half of the nineteenth century; its maker is unknown. (Photograph and Notes by Thomas B. Greenslade, Jr., Kenyon College).