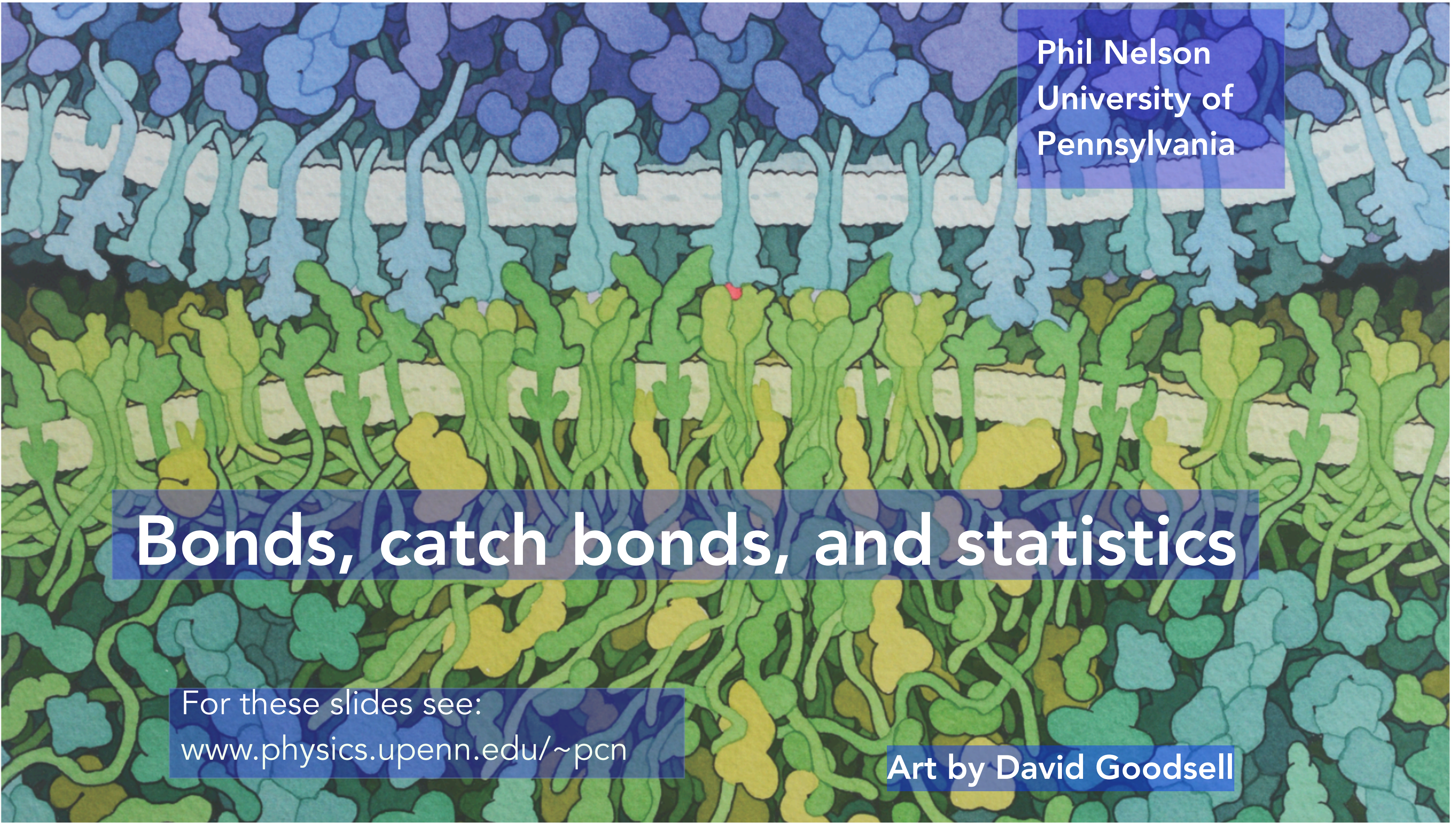


Bonds, catch bonds, and statistics

Phil Nelson
University of Pennsylvania

For these slides see:
www.physics.upenn.edu/~pcn

Art by David Goodsell

Who

Students in my class are mostly 2d/3rd year undergrads. Half in various Engineering majors, the rest mainly Biochemistry, a smattering of Physics and Chem. *They have had a year of intro Physics* and most have had a year of intro Chem.

What

Before this module, students need exposure to several topics never mentioned in first-year Physics courses:

- What is a probability distribution.
- What is the expectation of a random variable.
- Specifically what is the Geometric distribution: $\mathcal{P}(j) = \xi(1-\xi)^{j-1}$
- Rudiments of coding (we use Python; MATLAB is equivalent) and graphing.
- Specifically what is a semilog plot and what does it help us to see.

Why

Next slide. This is critical: They'll work if you can ignite some scientific curiosity with a puzzle.

Phil Nelson

"What we want is a story that starts with an earthquake and works its way up to a climax." — attr. to Samuel Goldwyn

Metro Goldwyn Mayer

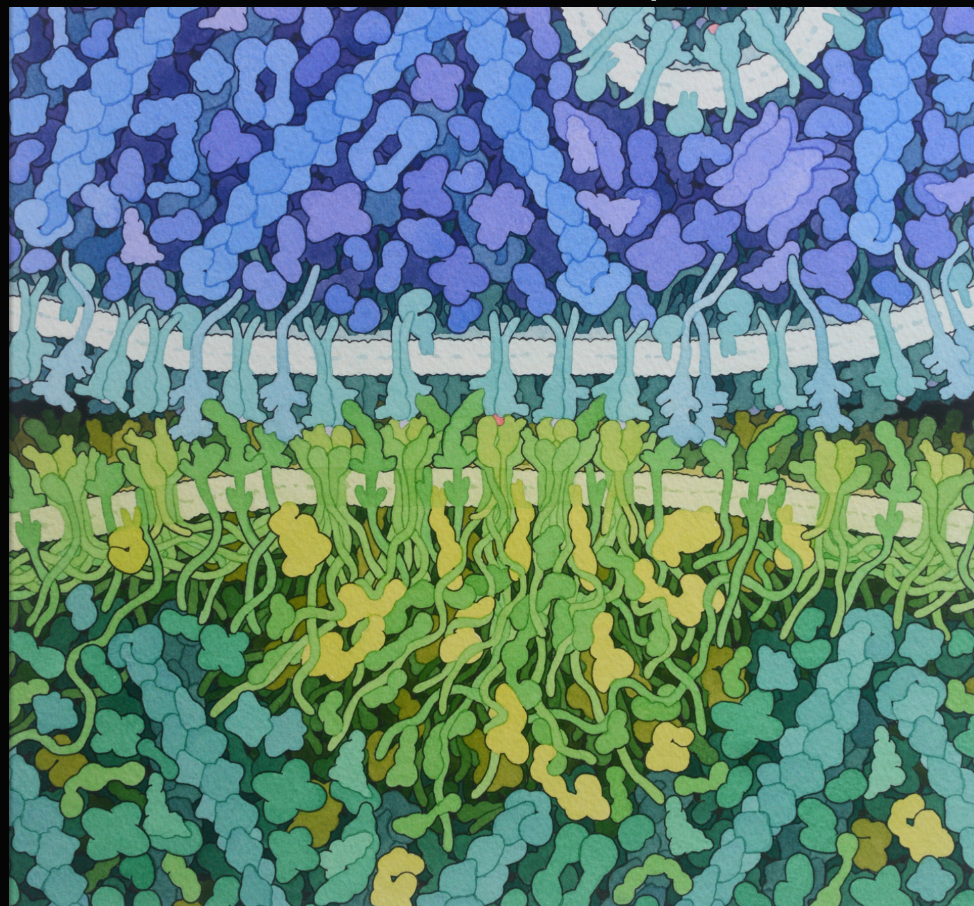
GRATIA ARS ARTIS

TRADE MARK

How can pulling two things apart strengthen their bond?

Phil Nelson

Why we all care about that question this year



Art by David Goodsell

Figure 6.11: [Artist's reconstructions based on structural data.] **T cell activation.** A key moment in the dialog between cells of the immune system, when an antigen presenting cell (*top*) is displaying a protein fragment (peptide, *red dot at center*) with MHC (*just above red dot*), and uses it to trigger activation of a T cell (*bottom*) through T-cell receptors (*just below red dot*). A signaling complex is starting to form in the T cell. [Art by David S Goodsell from coordinates in the RCSB Protein Data Bank: `doi: 10.2210/rcsb_pdb/goodsell-gallery-022`.]

Some goals

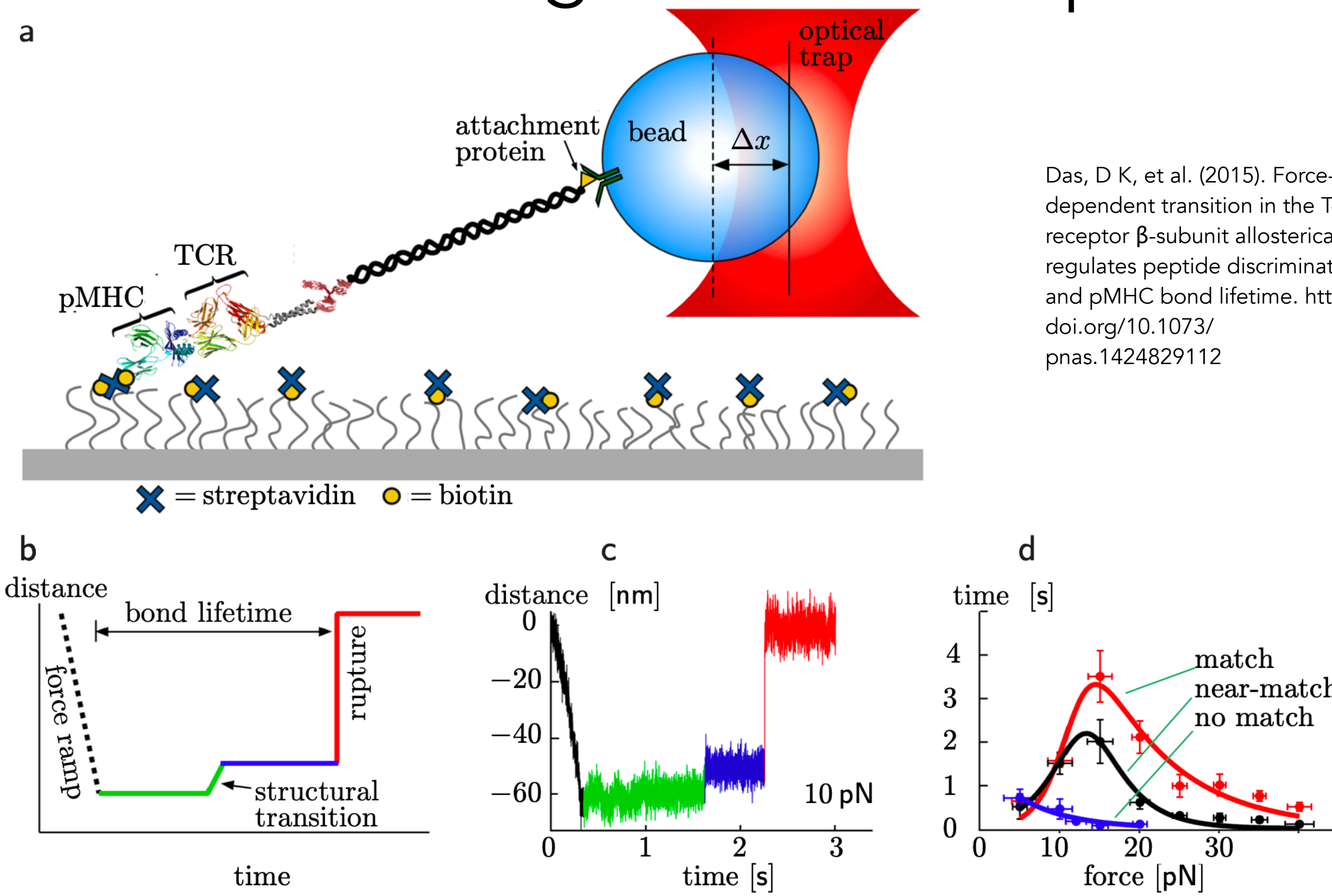
Cells communicate via mechanical forces.
Cells form bonds with neighbors, then actively test bond strength.
Some bonds surprisingly strengthen under stress (catch bonds).
That behavior can be understood and modeled.

That's Mechanobiology

Deeper level: I believe that biophysics is an ideal context to *teach people physics,* regardless of whether they think they'll become biophysicists later. It's way more motivating than, say... Atwood's machine.
First-year physics generally consists of a semester about mechanics followed by a semester about electricity, and neither feels particularly "life-like." Mechanics becomes much more relevant to cell and molecular biology when we acknowledge the incessant thermal motion that dominates the nanoworld. But that can quickly become abstract.
Emotional level: When you make a nontrivial scientific animation yourself, you never forget it.

Phil Nelson

Catch bonding in T-cell receptors



Das, D K, et al. (2015). Force-dependent transition in the T-cell receptor β-subunit allosterically regulates peptide discrimination and pMHC bond lifetime. http://doi.org/10.1073/pnas.1424829112

Figure 6.12: [Schematics; experimental data.] **In vitro catch bond assay** investigating the binding between a T cell receptor (indicated by *TCR*) and the peptide-major histocompatibility complex that it recognizes

Start out with Brownian with drift

Everything that follows flows from *one little line of code*:

`if random( ) < 0.49:` <– simulate a Bernoulli trial with probability 49%

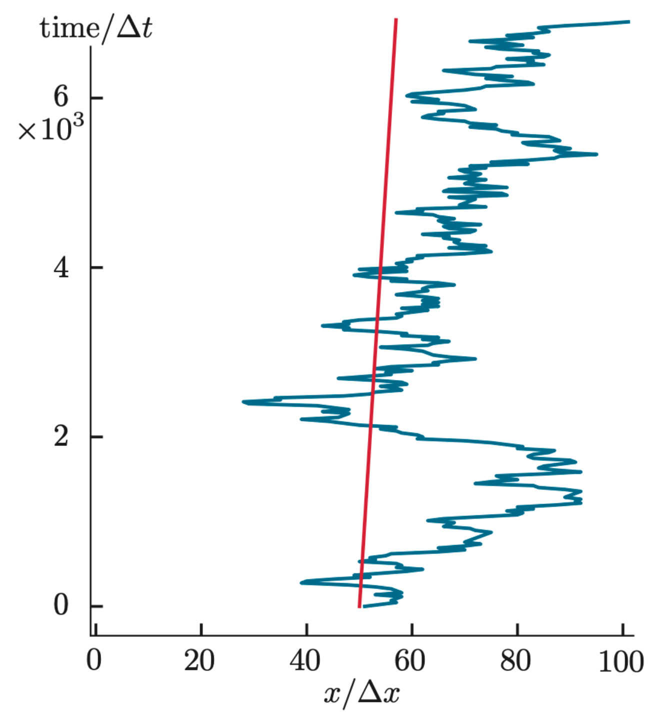
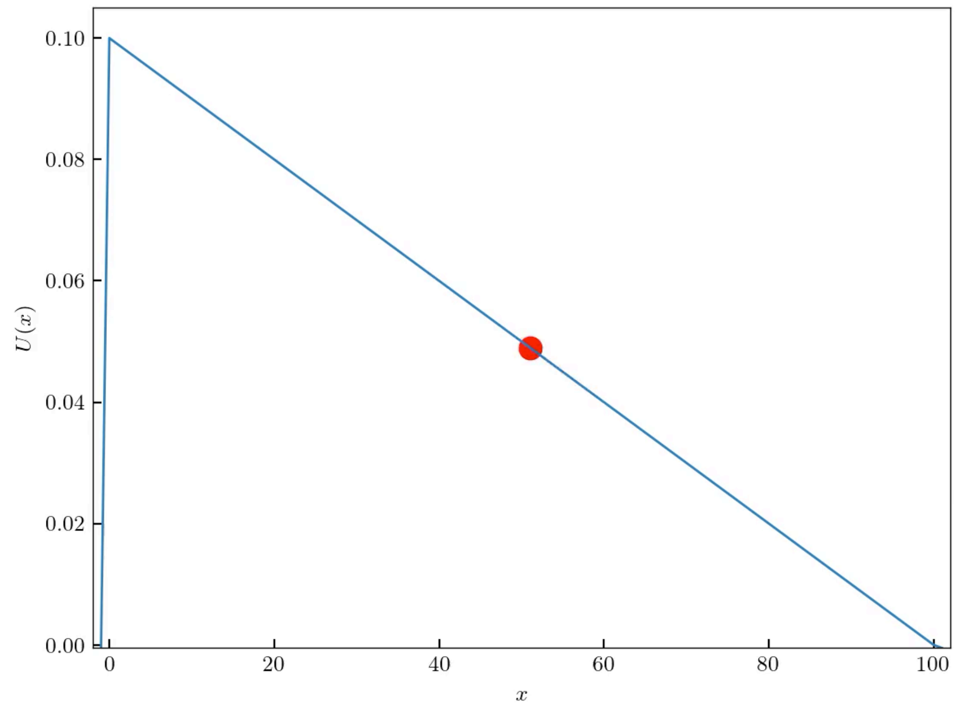


Figure 6.1: [Computer simulation.] **Typical random walk trajectory under constant applied force.** Time runs upward in this graph and is given as multiples of Δt. Position is given as multiples of Δx. A force of magnitude $0.002\zeta D/\Delta x$ is applied, directed to the right (increasing x). The resulting drift motion involves many temporary leftward excursions, but with an overall drift to the right. The average displacement over many instances has constant velocity given by Equation 6.2 (*red line*).

Phil Nelson

Brownian with drift: The Movie



The walker is not “trying to get out.” It doesn’t even “know” that there is a way out.

The walker is not “creeping up toward the exit.” It’s just blundering around, and eventually it stumbles upon the exit. Meanwhile it often “wastes” lots of time on excursions in the “wrong” direction.

Phil Nelson

Brownian in a trap

Next upgrade from constant force to position-dependent force.

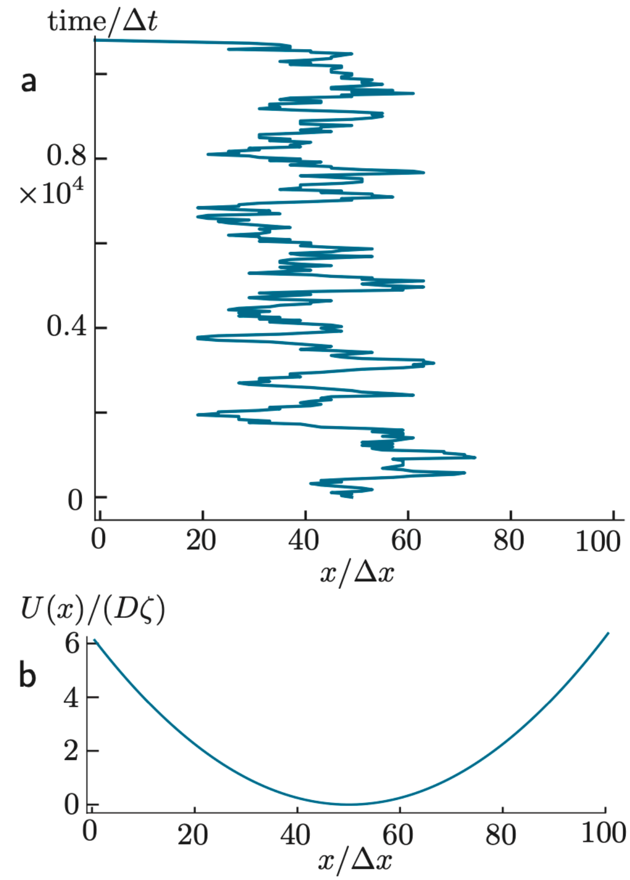
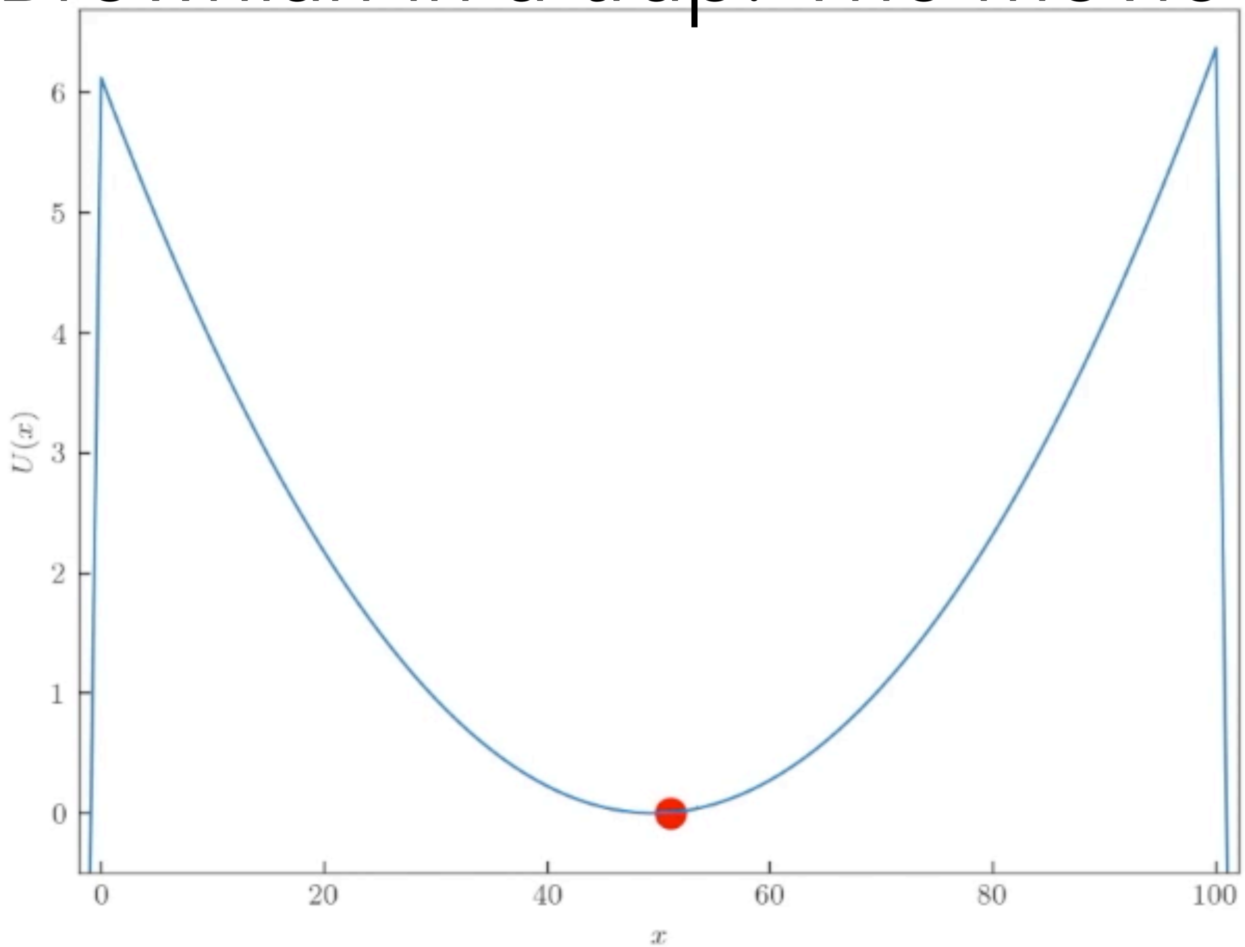


Figure 6.2: [Computer simulation.] **Random walk in a symmetric, harmonic potential energy trap.** (a) Although it is constantly pushed toward the center by a restoring force field, the walker eventually does arrive at $x = 0$. Media 6 displays this trajectory as an animation. (b) Potential energy trap giving rise to the walk in (a). The region most heavily visited by the walker aligns with the zone of low potential energy.

Phil Nelson

Brownian in a trap: The movie



Phil Nelson

Discover Boltzmann

A major result from a minor investment.

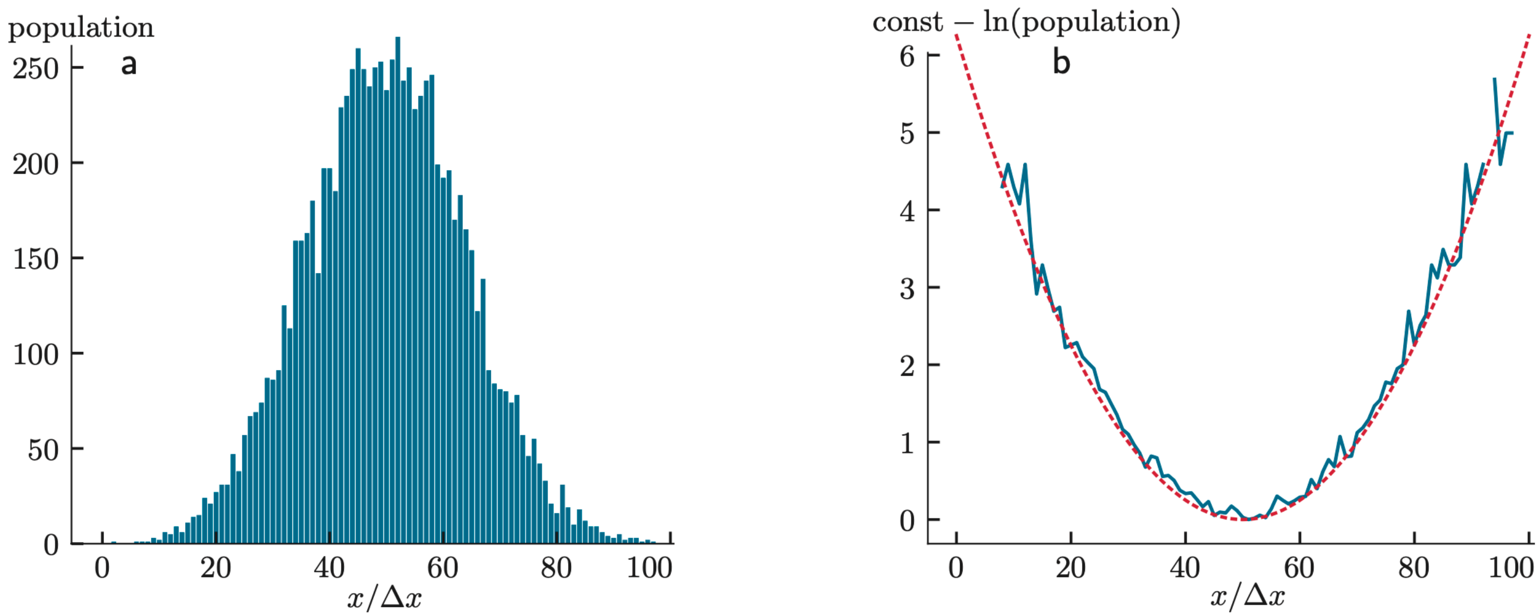


Figure 6.3: [Computer simulation.] **Distribution of 10 000 random walkers in a harmonic trap** after an initial equilibration time. (a) All walkers were released near the minimum of the trapping potential, but their distribution quickly approached the steady form shown here. (b) This semilog plot reveals the structure of the equilibrium distribution, by comparing it to $\exp(-U/(\zeta D))$ (*dotted red line*).

Phil Nelson

Discover Exponential distribution of escape times

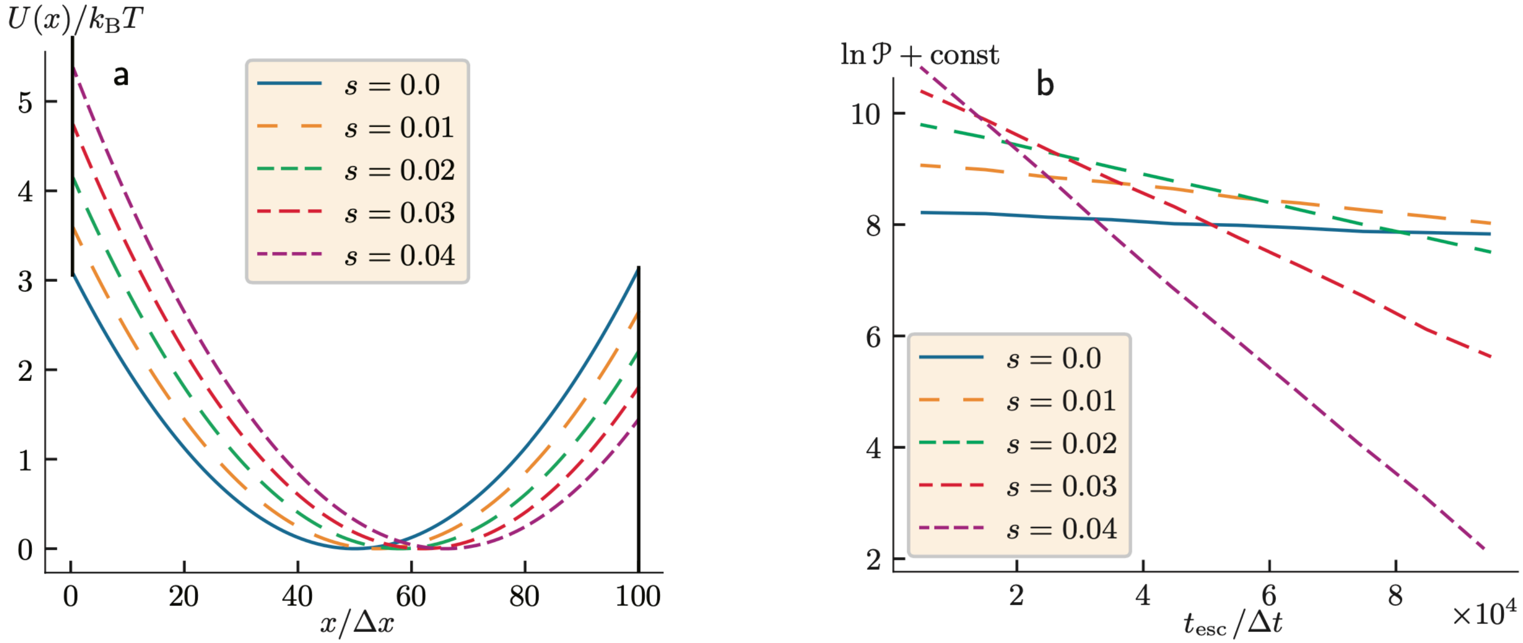
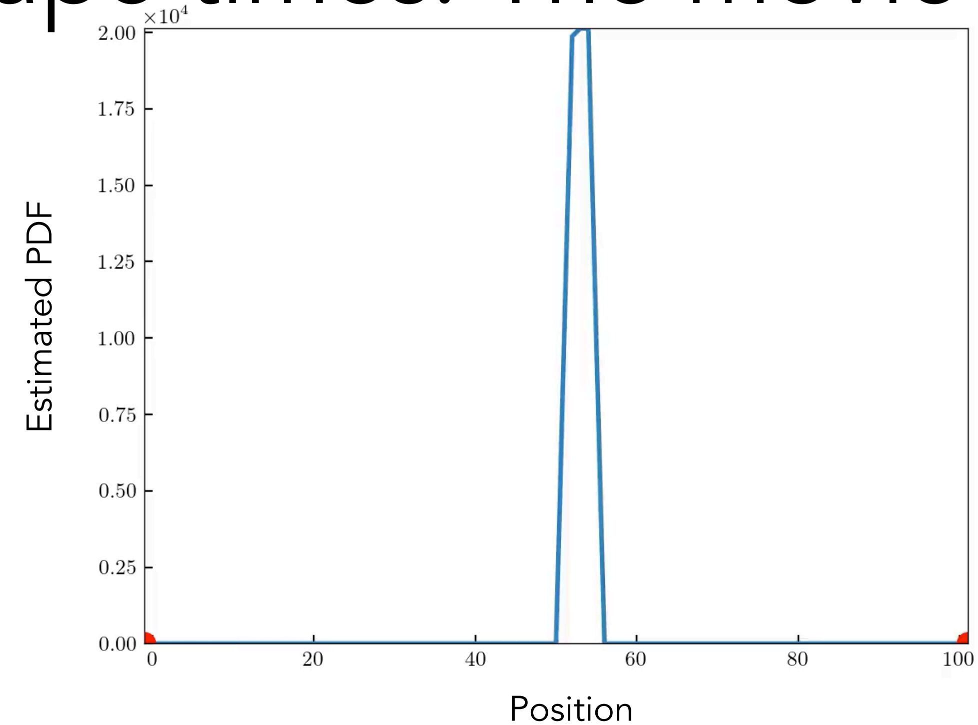


Figure 6.4: [Computer simulation.] **First-passage times for escape.** (a) Five different harmonic potentials. Each has a "hard wall" at $x = 0$ (*left vertical black line*). Each has a "cliff" at $x = 100\Delta x$ (*right vertical black line*) allowing "escape." The force parameter s is defined in Equation 6.7. (b) Semilog plot of the distributions of first-passage times. For each s value shown, 80 000 walkers were released near the center of the trap. Initially enough time was allowed to pass for the distribution to reach quasiequilibrium. Then a "clock" was started, and the times to escape after that moment were recorded. The figure shows a histogram of those times.

Escape times: The movie



Right dot: The mean rate of escape over the barrier is constant.
After an equilibration time, the probability distribution approaches a form that is independent of the initial distribution.
Probability then “leaks out” slowly over the cliff, because the region just inside the cliff is so rarely visited.

Phil Nelson

Discover Arrhenius law

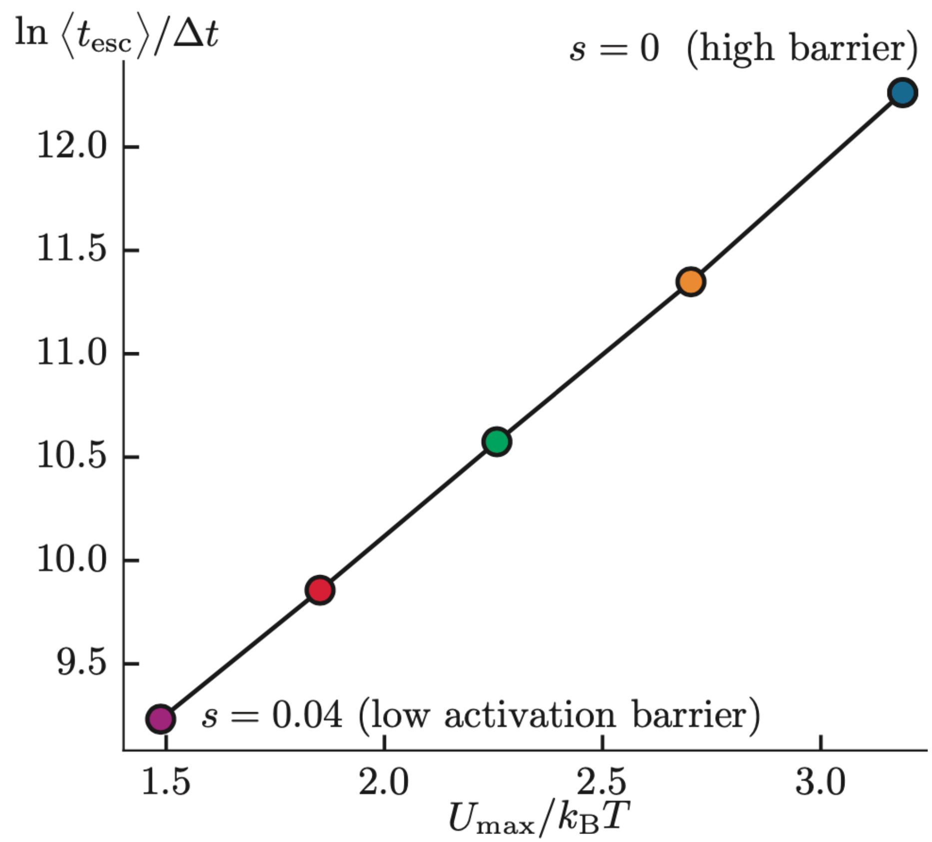
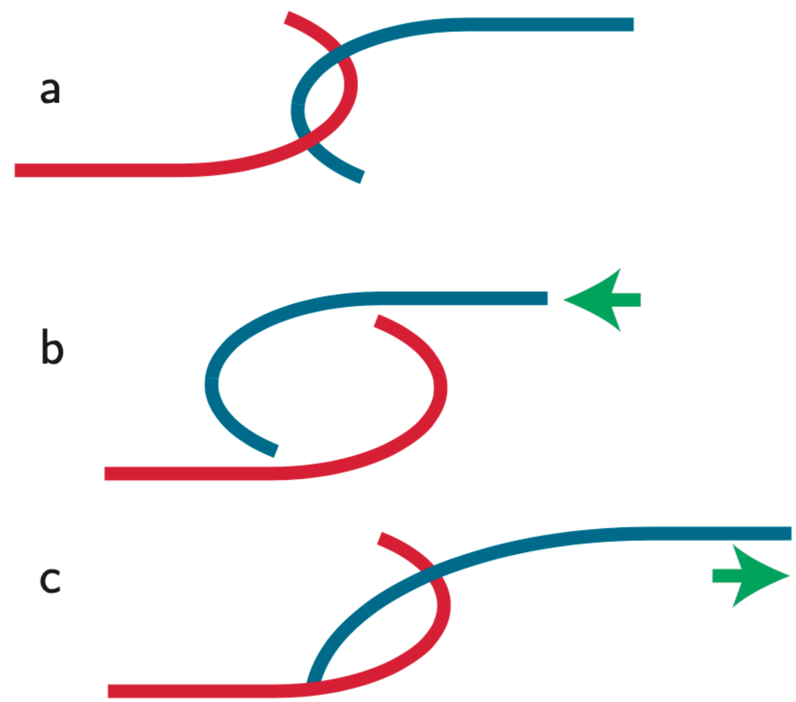


Figure 6.5: [Computer simulation.] **Mean first passage time versus energy barrier.** This semilog plot illustrates the general rule that, for a simple 1-step escape problem, mean first passage time is simply a constant times $\exp(U_{max}/k_B T)$. Values were calculated from the slopes of the lines in Figure 6.4b (or alternatively, via the procedure in Section 6.4′ on page 146).

Phil Nelson

Catch bonding via the Velcro effect

Figure 6.6: [Metaphor.] **Mechanical model of a catch bond.** (a) Two deformable hooks are linked. A weak spring keeps them under slight tension (*not shown*). (b) However, thermal agitation can move them together, against the weak spring, far enough to disengage. (c) An external pulling force can discourage that escape pathway. Then the hooks stay engaged unless the external force is so large as to straighten one or both of them (the alternate pathway to escape).



Phil Nelson

Two escape routes can respond differently to applied force

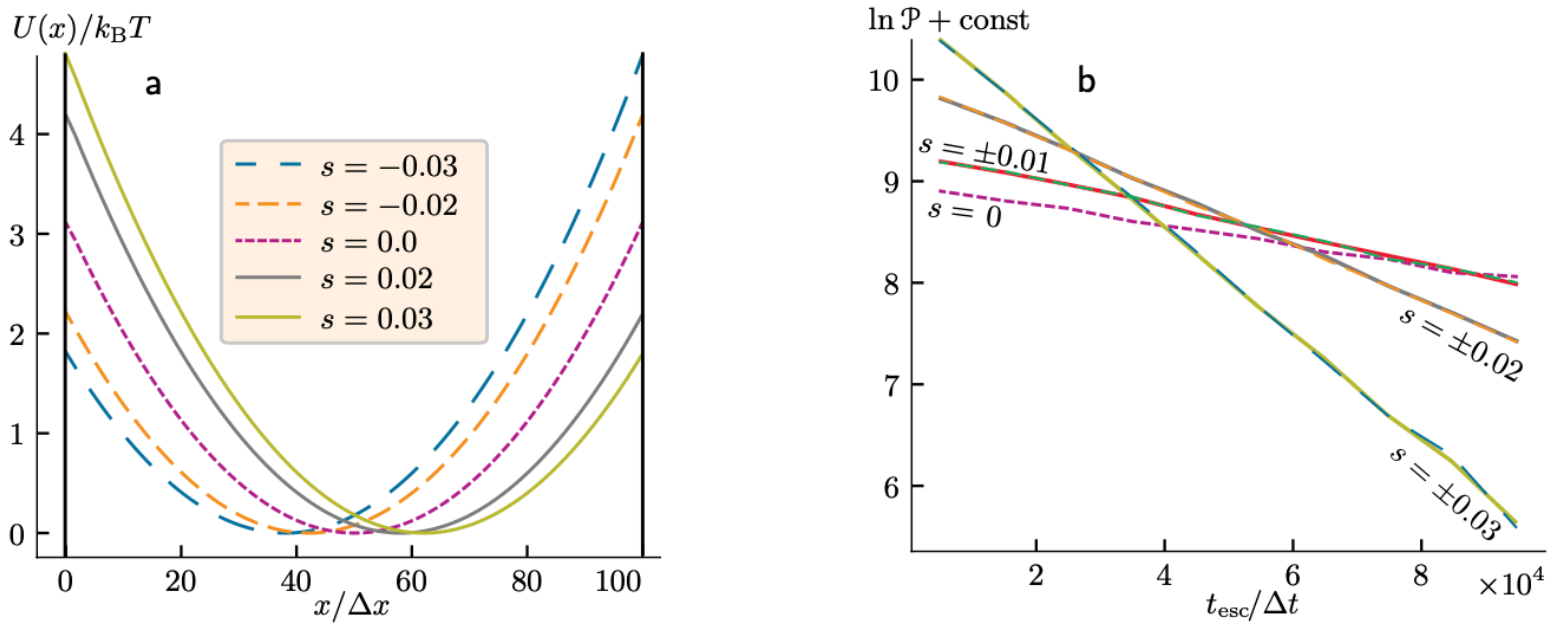
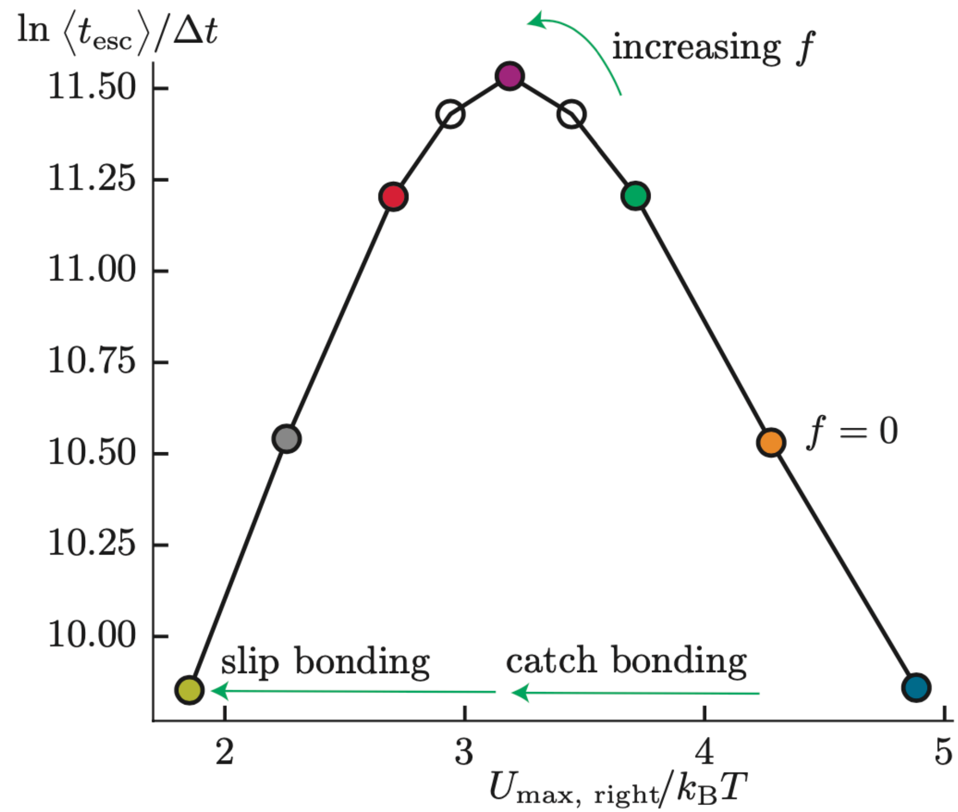


Figure 6.7: [Computer simulation.] **Multiple escape routes.** 80 000 walkers were again released, but this time they could "escape" either to the left or right side of the harmonic trap. (a) Potential energy functions. Negative values of s correspond to easier escape to the left; positive values correspond to easier escape to the right. (b) Semilog plot of the distribution of first-passage times.

Phil Nelson

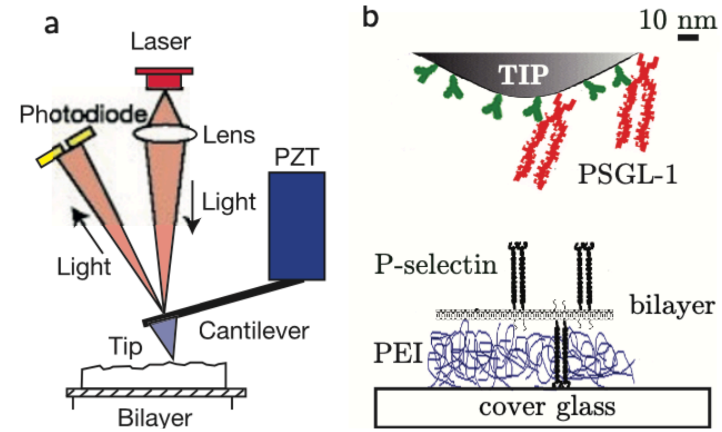
Discover catch bonding

Figure 6.8: [Computer simulation.] **Mean bond lifetime is controlled by the lowest energy barrier.** See text. The colors correspond to those in Figure 6.7. We imagine a system in which the orange dot corresponds to zero external force. Imposing an external force directed to the right then lowers the activation barrier $U_{\mathrm{max,\,right}}$ for escape to the right, and hence moves to the left on this graph. Small external forces increase bond lifetime (catch bonding, *green and purple dots*), whereas at larger forces lifetime decreases (slip bonding, *red, gray, and olive dots*).



Phil Nelson

Catch bonding is observed in leukocytes



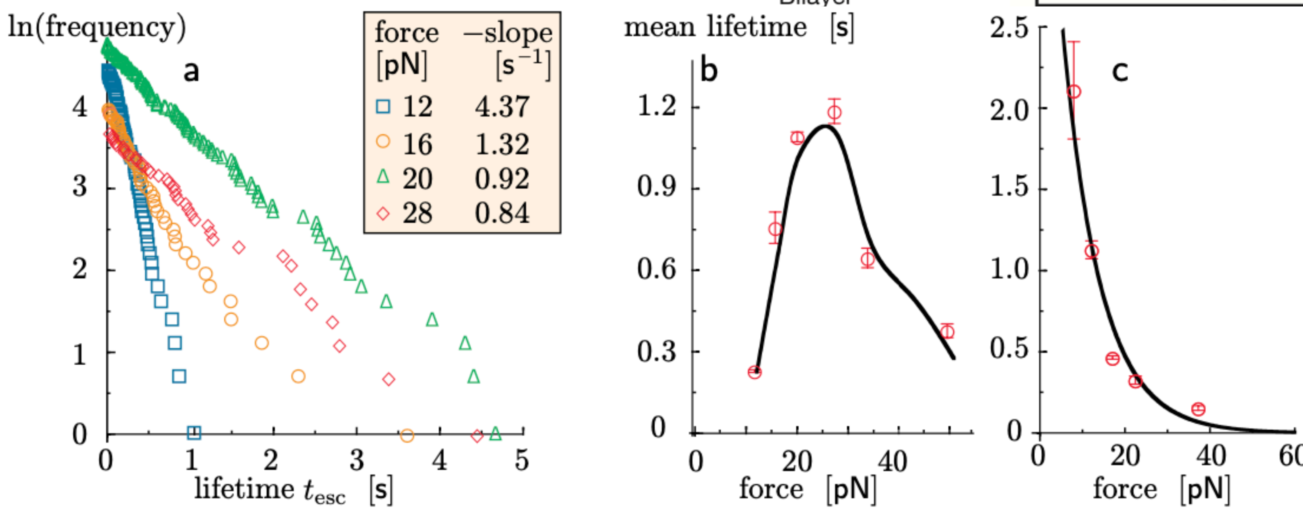
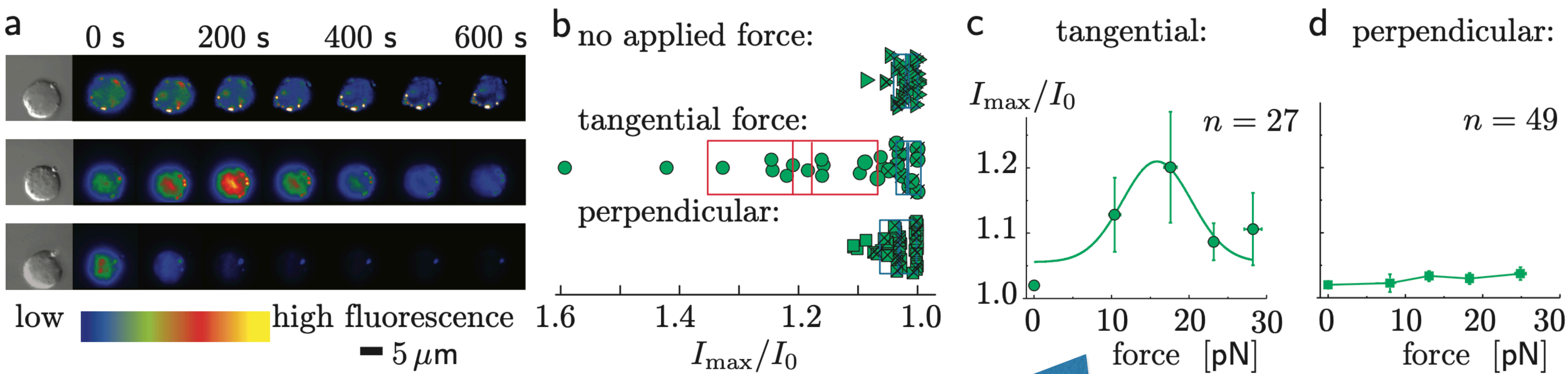


Figure 6.10: [Experimental data.] **Bond lifetimes in the experiment of Figure 6.9.** (a) Semilog plot of the number of events with a lifetime of t_{esc} or more versus t_{esc} for PSGL-1 binding to P-selectin. Various constant pulling forces in the catch bond regime were applied. Compare the simulation results (Figures 6.4b and 6.7b). (b) Mean lifetimes $\langle t_{esc} \rangle$ estimated as -1/slope of the plots in (a). Compare the simulation results in Figure 6.8. (c) For comparison, a similar plot but PSGL-1 was replaced by an antibody; ordinary slip-bond behavior was observed. [Data from Marshall et al., 2003.]

http://doi.org/10.1038/nature01605

Catch bonding is functionally significant in T cell activation



T cell activation does show catch-bond behavior similar to our little simulation! And surprise: The vector character of the force matters to the cell's function.

Feng, Y., et al. (2017). doi.org/10.1073/pnas.1703559114

Phil Nelson

Go long

Some of the ideas we have encountered are things that many scientists describe as "beautiful." What does that mean?

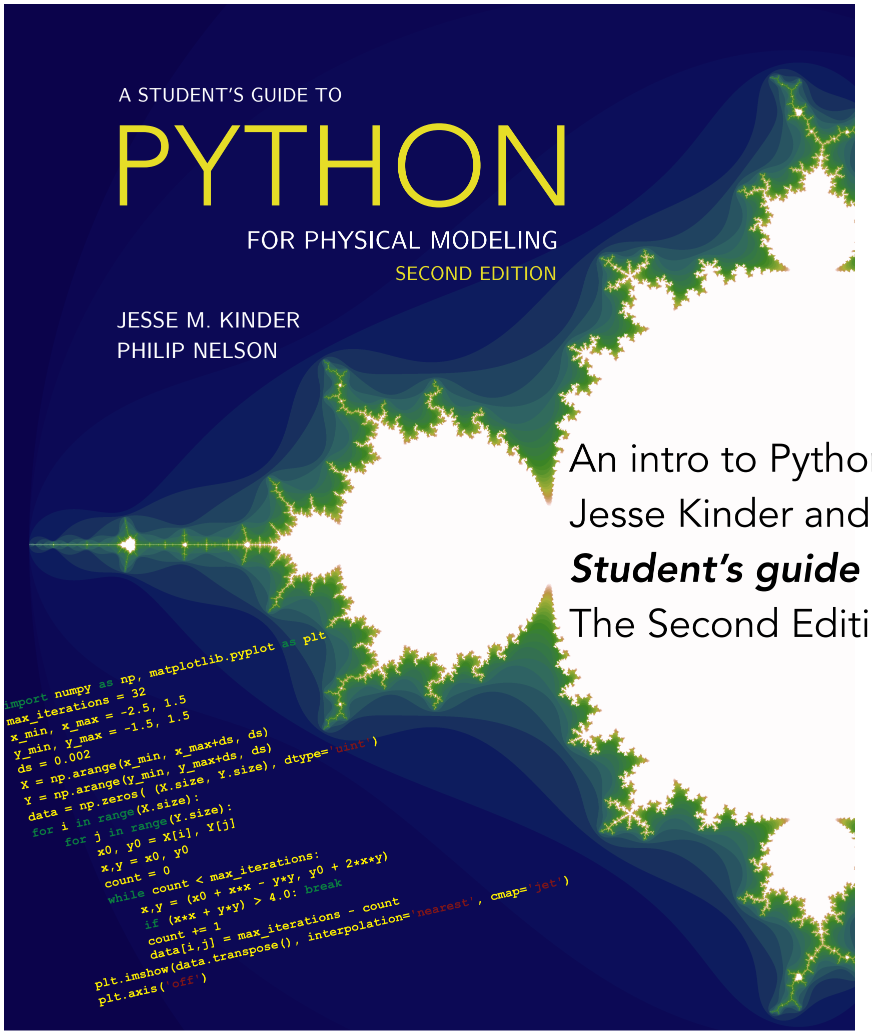
There are as many definitions as there are scientists, but I think many would agree that part of the answer is that a beautiful physical idea is ***surprising yet inevitable***; it may also be ***simple yet unexpectedly general.***

For example, *the biased random walk* has those qualities. We've seen how it gives a ***concrete, discovery-based approach to many things that are normally presented abstractly.***

It's amazing how a handful of basic concepts can be used to understand myriad problems at all levels, in both life science and physical science.

Phil Nelson

More



Material presented today will appear in a forthcoming textbook:

P. Nelson
Physical models of living systems 2d Ed.
The chapter discussed here is freely available:
`https://repository.upenn.edu/physics_papers/660`

An intro to Python coding is already available:
Jesse Kinder and P. Nelson
Student's guide to Python for physical modeling
The Second Edition is in production at Princeton U. Press.

CEMB Center for Engineering MechanoBiology

NSF CMMI–15-48571

Phil Nelson