Bonds, Catch Bonds, and Statistics

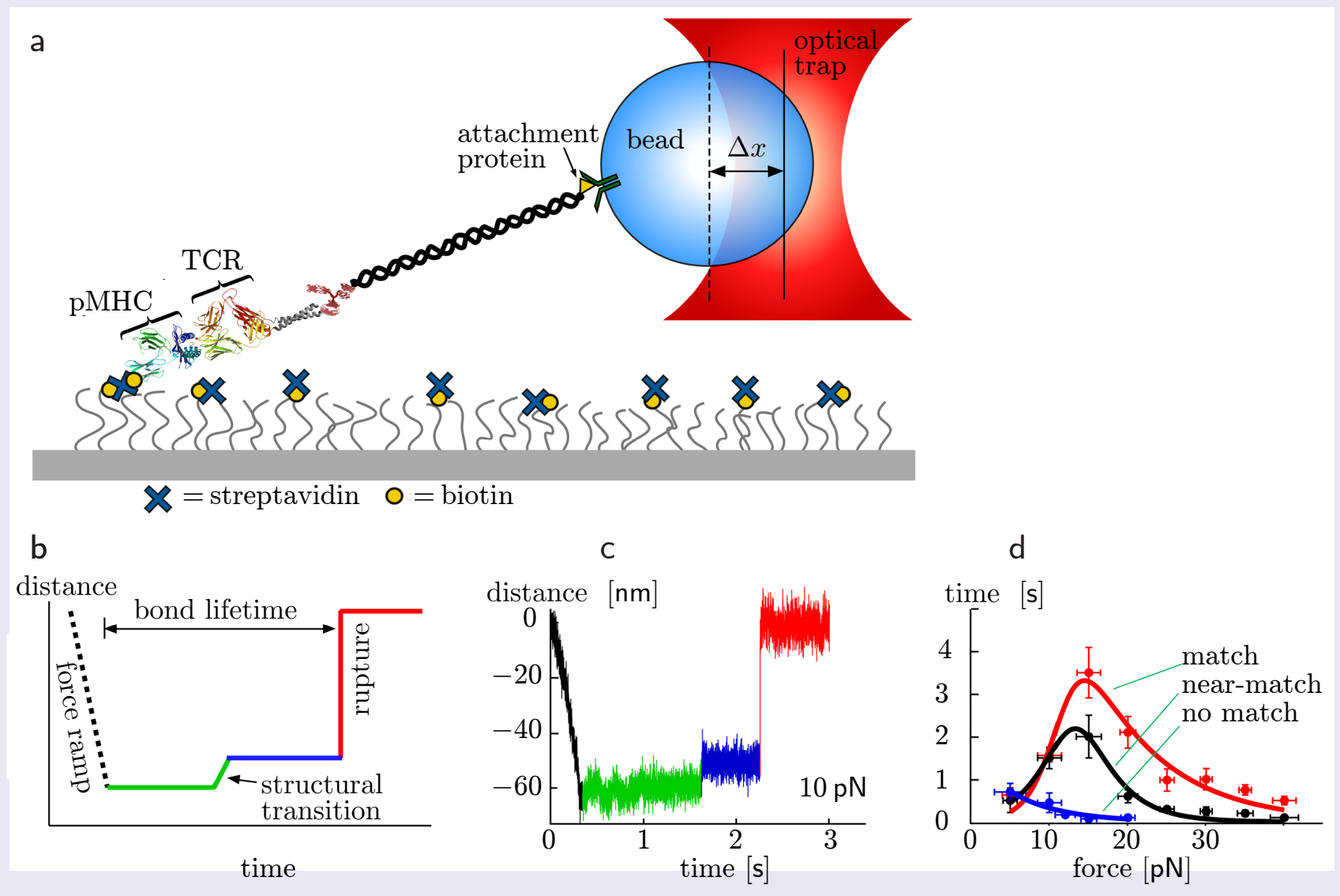
Philip C. Nelson

Dept.of Physics and Astronomy, University of Pennsylvania
`https://www.physics.upenn.edu/~pcn`

Catch Bonding

T cells must exercise exquisite judgement. Every cell displays tens of thousands of normal ("self") peptides; even a sick cell displays only a few abnormal ("non-self") ones. So even a tiny false-positive recognition rate would cause the immune system to attack our cells indiscriminately. (Indeed, autoimmune disorders do involve such errors, but they are rare.) How can immune recognition be so very accurate?

One aspect of the problem concerns binding between a T cell receptor (indicated by *TCR*) and the peptide-major histocompatibility complex that it recognizes (*pMHC*). Surprisingly, for a cognate peptide the bond lifetime *increases* with applied mechanical pulling force (data from [2]); the T cell measures this lifetime to determine if a match has been found.



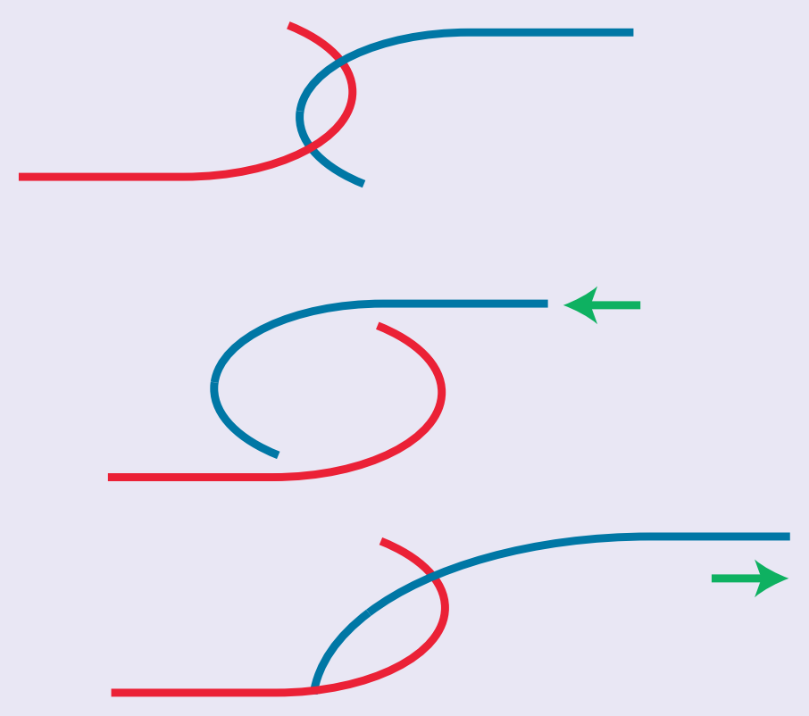
Overview

Education research shows that students engage better when an instructional storyline begins with a surprising claim about a topic important in their own lives. Today, everyone understands the importance of immune response to health. Also, most students find it paradoxical to be told that some bonds strengthen under applied pulling force. So the recent discovery of catch-bond behavior in T-cell activation is a very good starting point to motivate study of many biophysics ideas.

To understand the claim, we must introduce the notion of random walks on energy landscapes. Rather than the elaborate and technical Kramers theory, however, students can readily perform simple simulations. The results include memorable animated graphics that yield conceptual insight into bond formation and breakage, isomerization, and so on. Abstractions such as Boltzmann distribution and exponentially distributed lifetime emerge as concrete consequences of simple rules, and the origin of catch bonding behavior is clear when multiple unbinding routes are available.

Here I sketch a module suitable for installation into an advanced undergrad-level general Biophysics course [1]. Students wrote their own simulation codes from scratch to reproduce and extend figures in this poster.

A Mechanical Model with Catch-Bonding Behavior

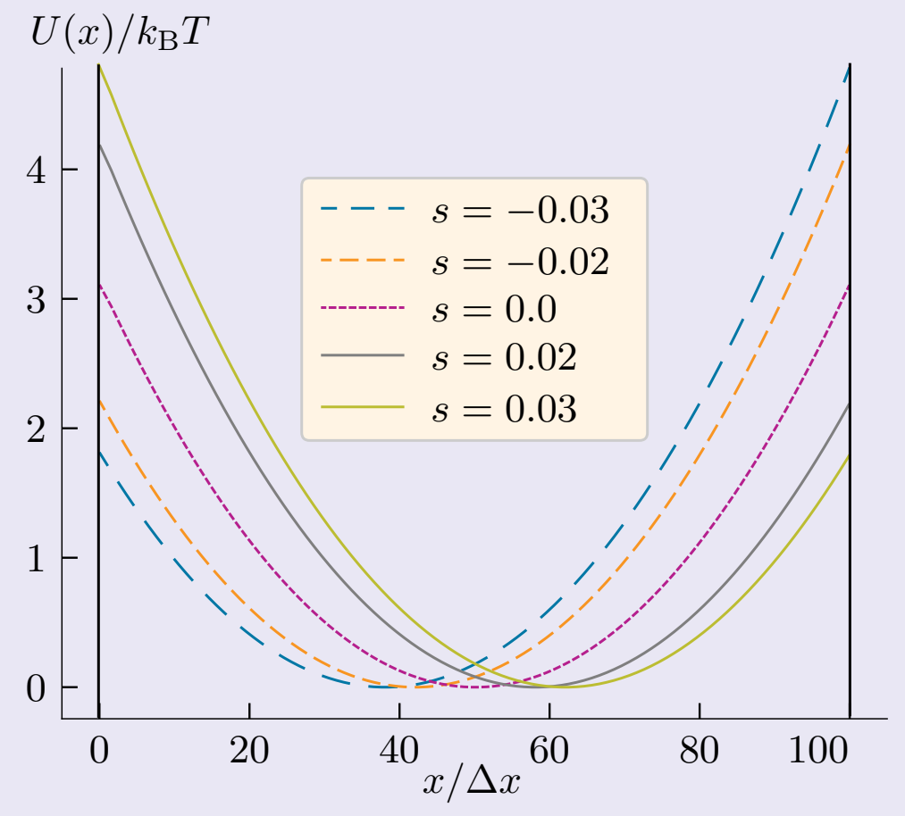


Two interlocking hooks. . .

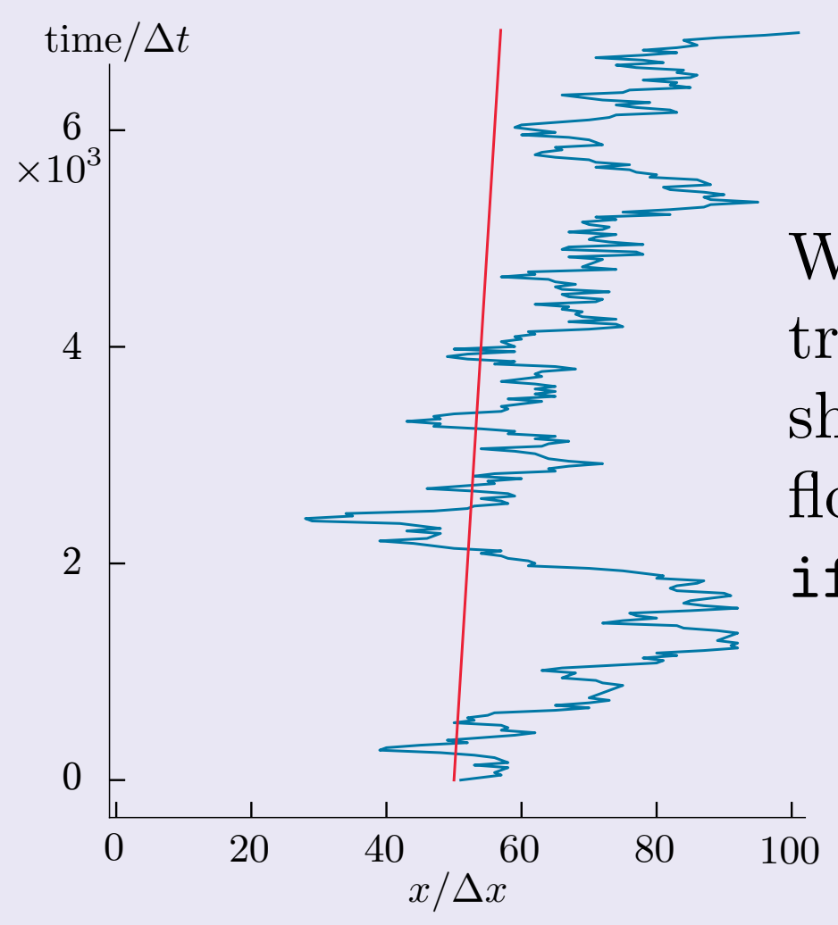
Can disengage either by pushing. . .

Or by pulling hard enough to deform them. Nature has already invented this system, for example, in burdock seeds.

A simple modification to the preceding model interprets "particle" position as relative displacement of the two hooks, and replaces the hard wall at the left by an alternative exit.



Warm up: Random Walks on an Energy Landscape



We begin by simulating a random walk with drift (as in electrophoresis). Students are impressed to find that an extremely short code generates physically interesting behavior: Everything flows from simulating a Bernoulli trial with probability P via

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if random( ) < P:
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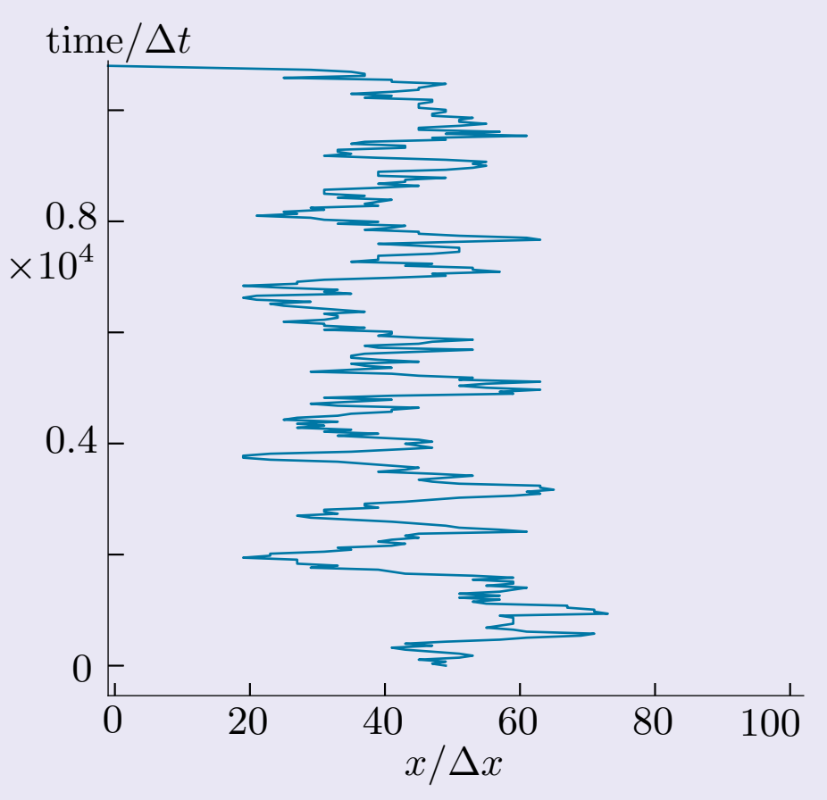
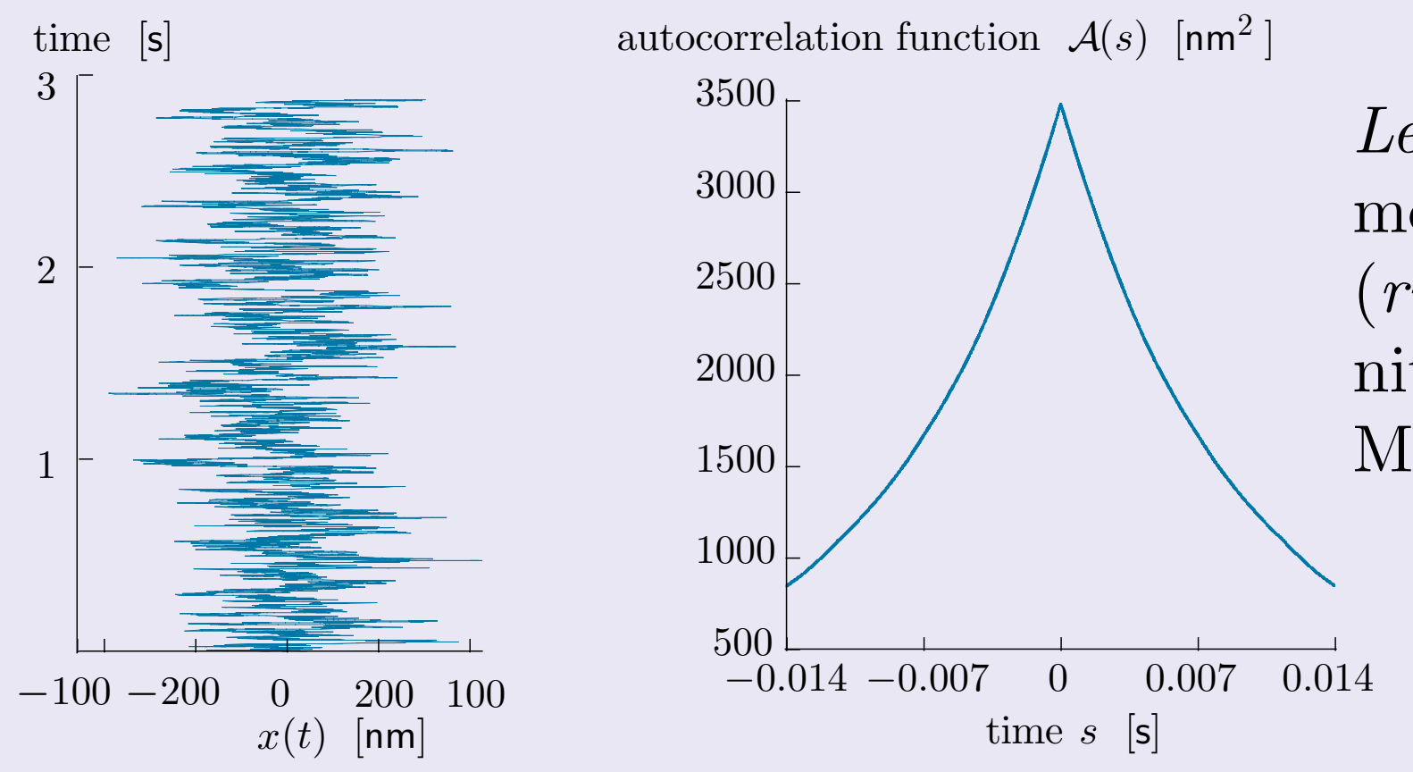
Next, we interpret the constant force in electrophoresis as minus the gradient of a potential energy, and generalize to nonlinear energy profiles, for example, a harmonic trap (*right*). Although the walker generally stays close to the minimum-energy position, it can eventually wander arbitrarily far (*top*).

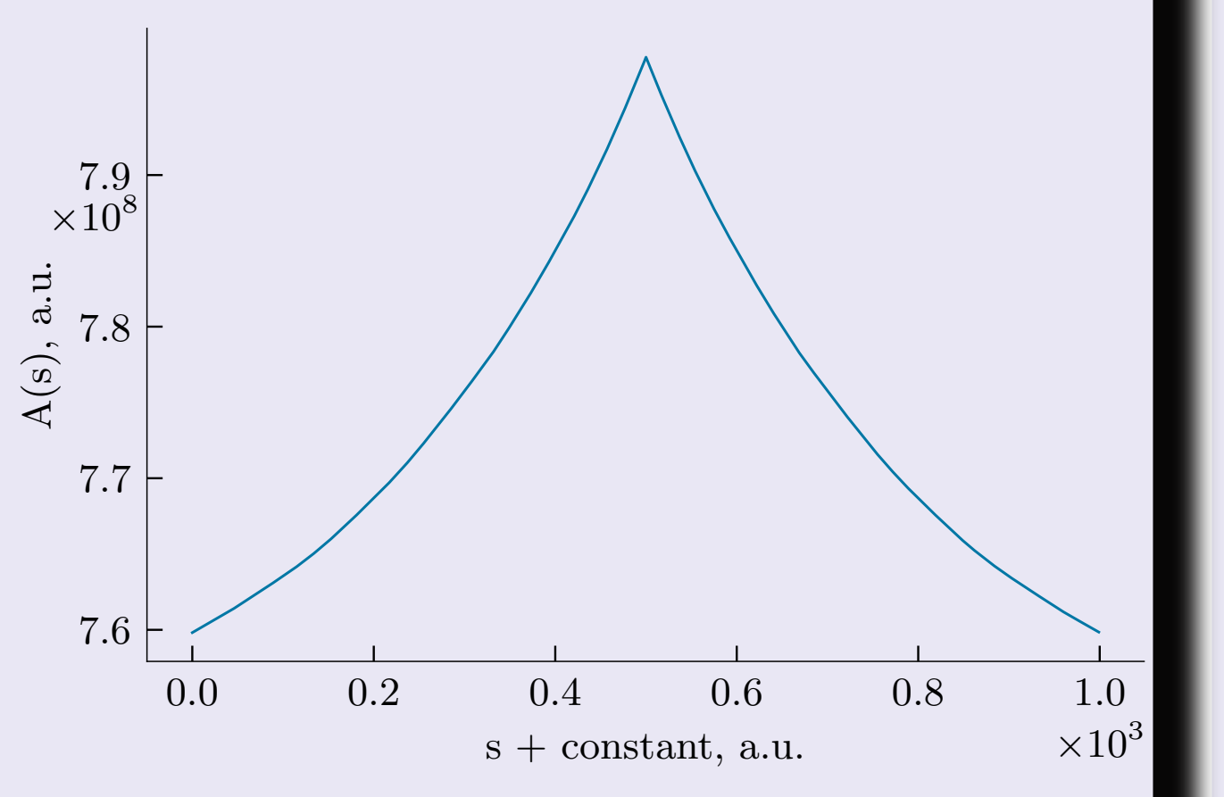


Autocorrelation and Optical Trap Calibration

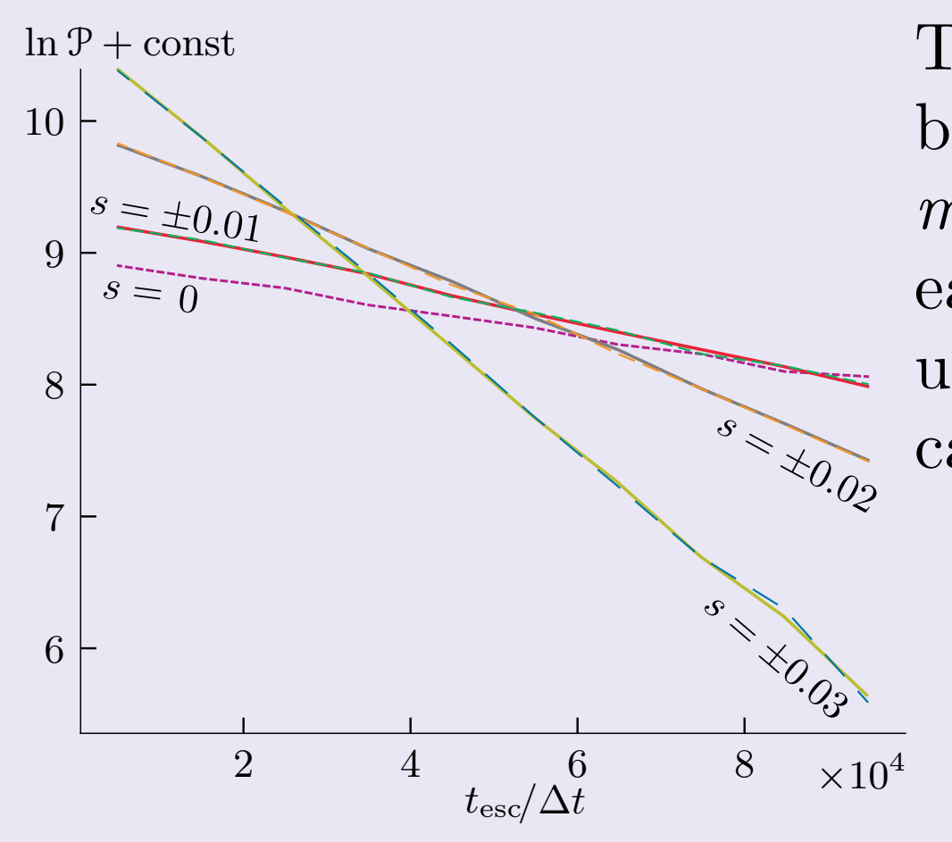


Left: Real time-series data on tethered particle motion may look like unstructured noise, but (*right*) its autocorrelation function has a definite structure. (Data kindly supplied by J. van Mameren and C. Schmidt.)

Students find the autocorrelation empirically from their own simulation, and observe its qualitative connection to data. Then they see how to extract the physical parameters (trap stiffness and mobility) by fitting such data to the model.

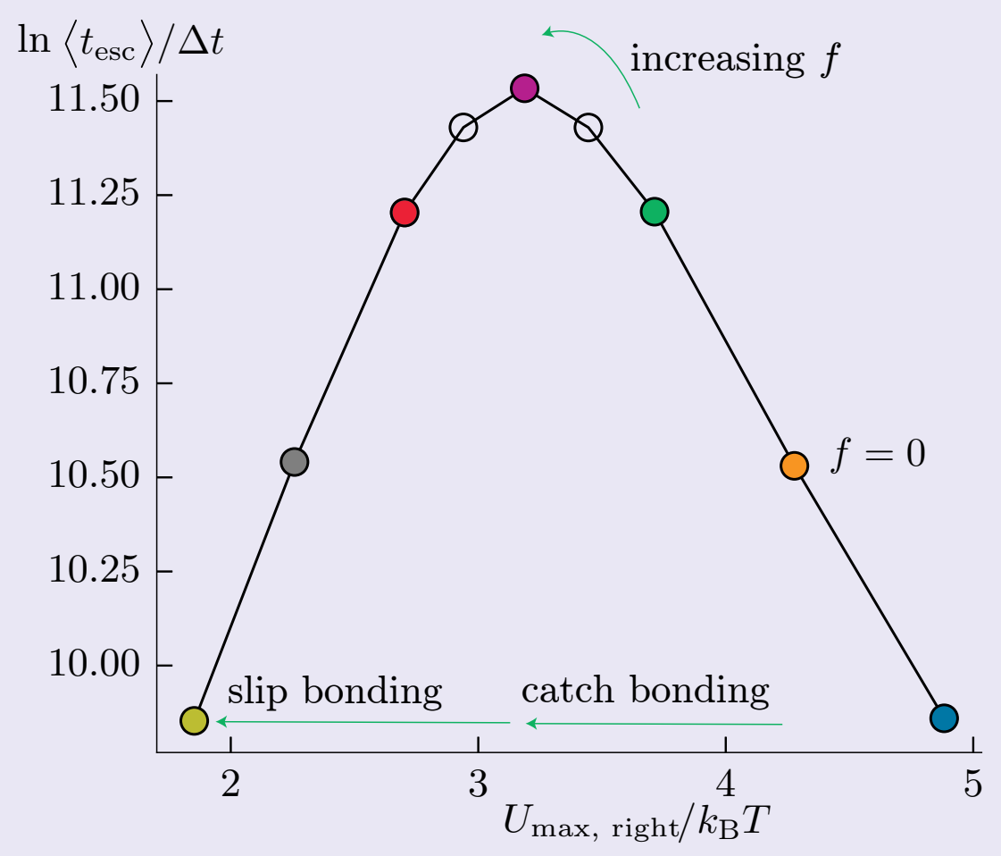


Discover Catch-Bonding in the Model of Random Walks on a Landscape

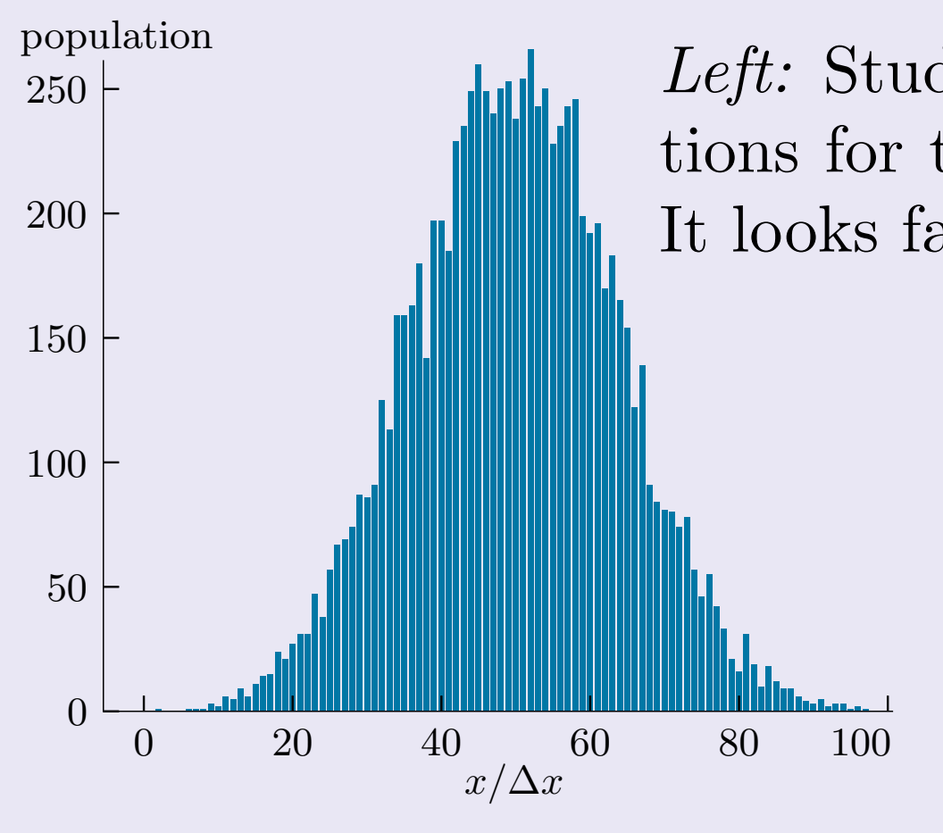


The bridge from the mechanical model to molecular catch-bonding is to understand the "strength" of a bond as its *mean lifetime.* When students simulate a random walk on each of the landscapes in the preceding panel, they find—unsurprisingly—a shortening of mean waiting time for escape with either positive or negative applied force.

But a real system won't in general be symmetrical. Zero applied force may favor one escape route as shown here. In that case, external applied force can suppress the favored exit before it begins so enhance the disfavored one, leading to an initial *increase* in bond lifetime—the catch-bond phenomenon.

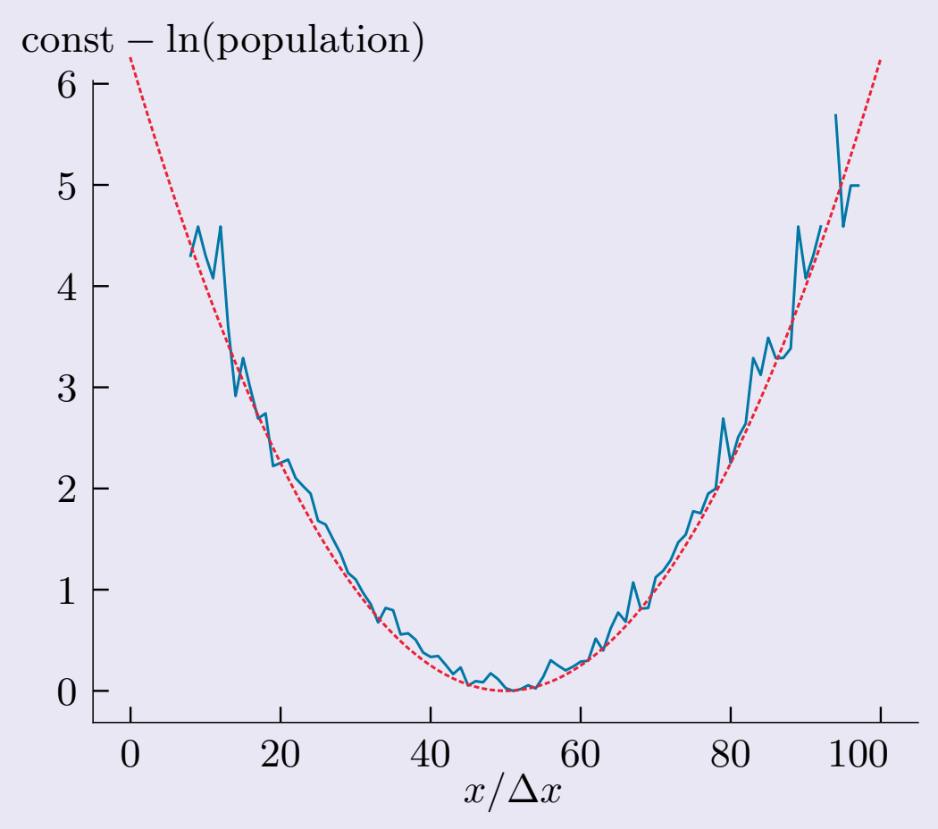


Discover the Boltzmann Distribution and Einstein relation

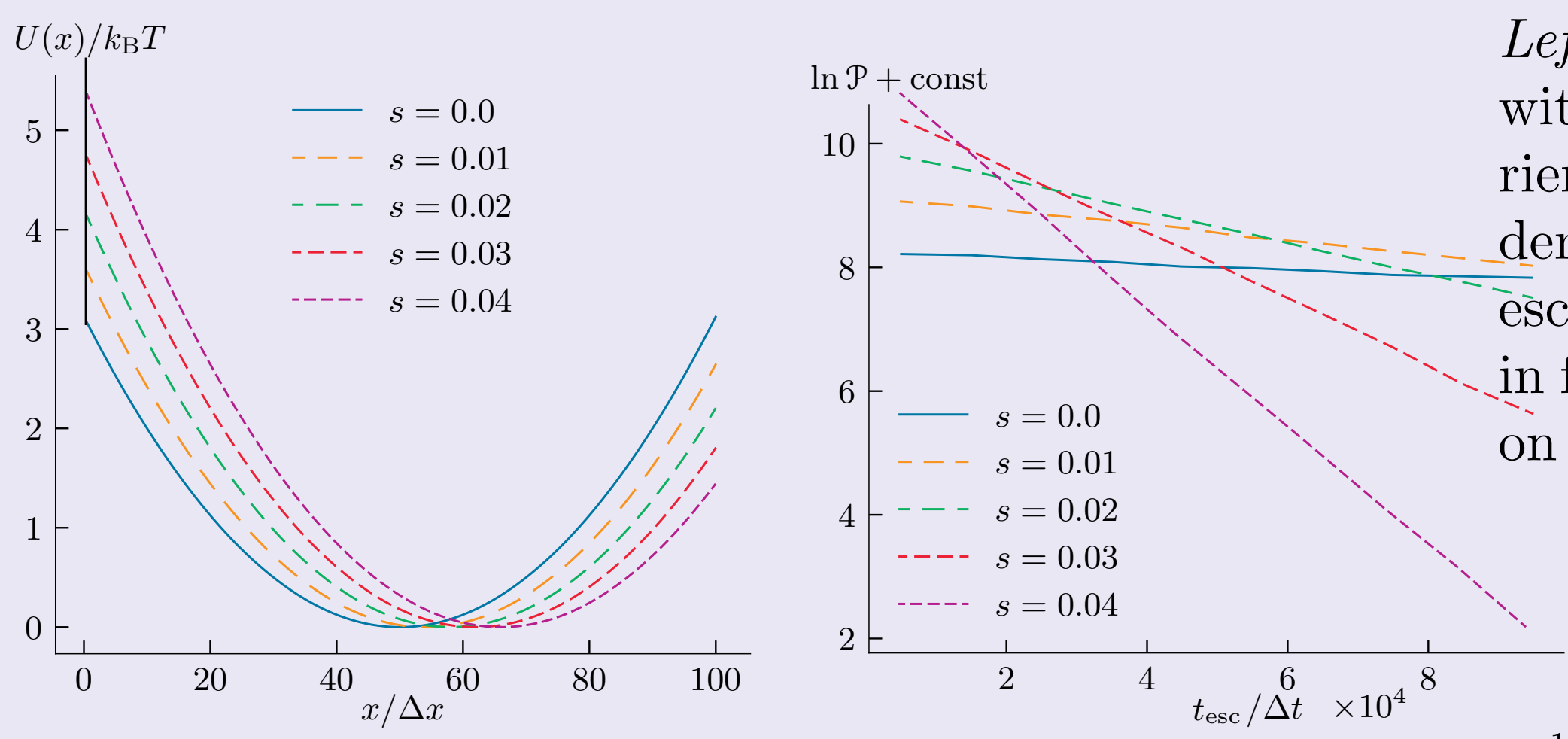


Left: Students discover empirically the full distribution of positions for the harmonically-trapped particle after equilibration. It looks familiar—is it a Gaussian?

A semilog plot of the estimated probability density function (*blue*) indeed superimposes on a parabola (*red*). Moreover, students find empirically a universal relation between the particle's mobility (an input parameter for the simulation) and the trap stiffness—the Einstein relation.

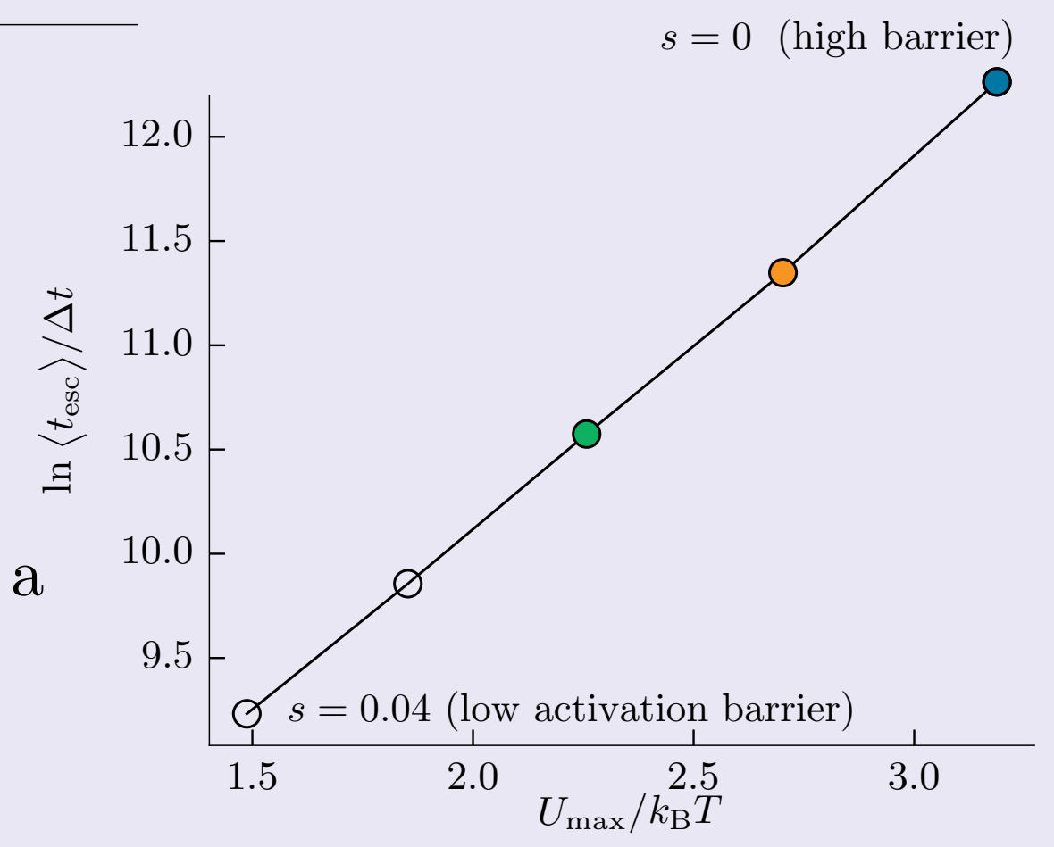


Discover Exponential Waiting Time Distribution and Arrhenius Law



Left: Five energy profiles, each with a hard wall on left and a barrier to escape on right. *Right:* Students empirically find the PDF of escape times is always exponential in form, with mean time depending on the energy profile.

In fact, the mean escape time found by simulation has a very simple relation to the barrier height.



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