The other half of western civilization: An experiment in freshman science teaching

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How many cultures?

Literary intellectuals at one pole--at the other scientists, and as the most representative, physical scientists. Between the two a gulf of mutual incomprehension ... a curious distorted image of each other.

CP Snow, in The Two Cultures and The Scientific Revolution
(Cambridge University Press, 1959)

Could there be as large a gulf within science itself?

The "mathematical sciences"
(e.g, physics)

The "non-mathematical sciences"
(e.g, biology)

There is a widespread (almost trite) sentiment that this gulf between the physical and biological sciences needs to bridged, and that now is the right time to do this.

"The biology of the 21st century will be a more quantitative science."
"The greatest challenges need to be met by interdisciplinary collaborations."
"The genome and the computer have revolutionized how we do biology."
"As we address system-level questions, we move beyond what we can do intuitively, and need more mathematical tools."
"Mathematics will be biology's new microscope."

There is much less agreement about what all of this actually means, even in principle.

"There's something happening here, what it is ain't exactly clear ..."
(Stephen Stills, Buffalo Springfield, 1967)

Before we have a theory, let's look at the data ...

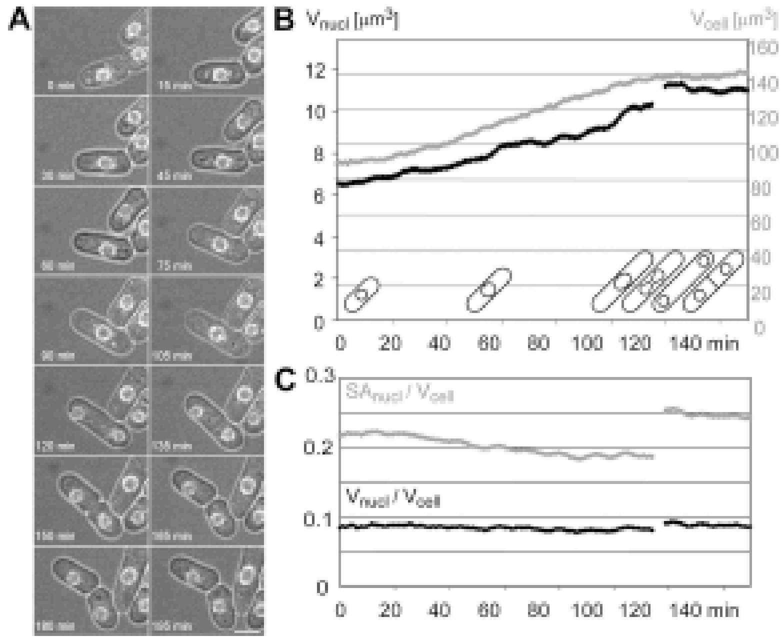


Figure 3. N/C ratio is constant throughout cell cycle. Cell cycle analysis of nuclear and cell size using time-lapse microscopy (6 z-sections/min). (A) Time points of a selected field from Video 1. (B and C) The graphs represent the median of a 10 min moving averages from 5 independent cells, analyzed for an entire cell cycle as shown by the cartoons. Average cell volume (gray) and nuclear volume (black) cells and the respective N/C ratios (gray: nuclear surface area/cell volume, black: nuclear volume/cell volume). Video 1 is available at http://www.jcb.org/cgi/content/full/jcb.200708054/DC1.

the availability and the targeting of newly formed membrane components from the ER, growth driven by volume increase would involve either nucleocytoplasmic transport or diffusion of smaller molecules through nuclear pores and sequestering within the nucleus. Two sets of experiments suggest that the NE expansion is a result rather than the cause of nuclear volume increase. First, it has been shown that NE-ER over-proliferation is not sufficient to increase nuclear size, but instead leads to an accumulation of NE sheets around the nucleus (Lum and Wright, 1995; Tange et al., 2002). Second, when blocking nuclear export of a subset of proteins for 90–150 min using leptomycin B (LMB), a specific inhibitor of the exportin crm1, nuclear size and the N/C ratio increase by 50% (Matsuyama et al., 2006; Fig. S2, available at http://www.jcb.org/cgi/content/full/jcb.200708054/DC1). This suggests that nucleocytoplasmic transport directly or indirectly alters nuclear size control, and contrasts with data from budding yeast, where 5–30 min of treatment with LMB had shown no obvious effect on nuclear size (Jorgensen et al., 2007). The differences in the results may be due to the more extended time course of drug treatment in our experiments. We further tested if the distribution of nuclear pores influences the N/C ratio. Cells deleted for *nup133b* and marked with the nucleoporin Nup107-GFP have less evenly distributed nuclear pore complexes (Bai et al., 2004), but the N/C ratio is not affected (unpublished data).

It is possible that nuclear volume could be controlled by some surrogate, such as amount of RNA or protein, numbers of ribosomes, or membrane content. In motoneurons and hepatocytes, cell size and nuclear size both correlate with the cellular RNA/DNA ratio, the expression of ribosomal genes, and general transcription rate (Sato et al., 1994; Schmidt and Schibler, 1995). Future studies will be required to dissect the molecular basis of nuclear size control in fission yeast.

A similar general cellular control that regulates nuclear growth in response to the amount of cytoplasm surrounding the nucleus may influence nuclear growth in other eukaryotes. However, differences in the cellular differentiation state and organismal developmental stage or the presence of a nuclear lamina, add more layers to N/C ratio control. Although we have shown that DNA content does not directly influence nuclear size, it might set a minimum to the size of the nucleus as suggested by the nucleoskeletal theory (Cavalier-Smith, 1982; Gregory, 2005), especially in small cells such as spores. For example, whereas wild-type spores have an N/C ratio of 0.076 ± 0.016 (see Fig. 1, A, B, and D), *wee1*[ts] spores have a 20% smaller cell size but only 8% smaller nuclei, indicating that a minimal nuclear size may have been reached (*wee1-50/wee1-50*, $n = 136$, N/C = 0.089 ± 0.017).

Nuclear size regulation could be influenced by several cellular functions such as nucleocytoplasmic transport, lipid

plates scanned one-quarter of the Poincaré sphere in 65 steps for ϕ and 64 steps for θ, a measurement which took over five hours. The rest of the data can be deduced from symmetry.

For each pair of angles, the photocurrent noise of both detectors after the PBS was simultaneously sampled 2.9×10^6 times. Noise statistics of the difference of the two photocurrents were acquired in histograms with 2048 bins and the optical intensities incident on both detectors were recorded as well (as dc current values). In Fig. 2, we show typical histograms at different angles on the Poincaré sphere. As the widths of the histograms largely vary from squeezing to antisqueezing ranges, there are two plots with the amplitude scale differing by more than 1 order of magnitude. The histograms labeled 1–3 are measured in the dark plane, which is perpendicular to the classical mean value of the state. Label 1 denotes the angle of maximum squeezing, while label 3 corresponds to the antisqueezing. Label 5 is the angle of the classical mean value, where the measured noise data are almost shot-noise limited. Because of the high number of samples, the measured histograms are smooth, and, at the same time, the number of bins makes it possible to resolve the large dynamical range of amplitudes, so no data interpolation was needed. We also plot histograms showing the electronic noise and the shot noise. Higher-order moments of the measured data were also computed, but we found no significant deviation from what is expected from a Gaussian distribution.

The reconstruction in each $(2J+1)$-dimensional invariant subspace can be now carried out exactly since it is essentially equivalent to a spin J [17]. After some calculations, one finds that

$$\varrho_J = \frac{1}{4\pi} \sum_{m=-J}^{J} \int_{\mathcal{S}_2} d\mathbf{n}' w_m^J(\mathbf{n}') \mathcal{K}_J(m - \mathbf{n}' \cdot \hat{\mathbf{J}}), \tag{4}$$

where the integration extends over the unit sphere $\mathcal{S}_2$ and the kernel $\mathcal{K}_J(x)$ is

$$\mathcal{K}_J(x) = \frac{2J+1}{4\pi^2} \int_0^{2\pi} d\omega \sin^2\left(\frac{\omega}{2}\right) e^{-i\omega x}. \tag{5}$$

From the exact solution (4), one can calculate any polarization quasidistribution [18]. From a computational perspective, the SU(2) Q function turns out to be the simplest, since in each invariant subspace it reduces to

$$Q(J, \mathbf{n}) = \langle J, \mathbf{n} | \hat{\varrho}_J | J, \mathbf{n} \rangle, \tag{6}$$

where $|J, \mathbf{n}\rangle = \hat{R}(\mathbf{n})|J, m = -J\rangle$ are SU(2) coherent states obtained by displacing the "ground" state $|J, -J\rangle$ over the sphere [19]. This definition is a straightforward generalization of the standard one for the harmonic oscillator. The Wigner function can also be evaluated, although with additional effort. Nevertheless, we do not expect these two quasidistributions to differ notably for the states we study here. We need only thus to calculate the matrix elements of the kernel $\mathcal{K}_J(m - \mathbf{n}' \cdot \hat{\mathbf{J}})$. The most direct way to proceed is to note that

$$\langle J, \mathbf{n} | \mathcal{K}_J(m - \mathbf{n}' \cdot \hat{\mathbf{J}}) | J, \mathbf{n} \rangle = \frac{2J+1}{4\pi^2} \int_0^{2\pi} d\omega \sin^2\left(\frac{\omega}{2}\right) e^{i m \omega} \left[\cos\left(\frac{\omega}{2}\right) - i \sin\left(\frac{\omega}{2}\right) \cos\chi\right]^{2J}, \tag{7}$$

where $\cos\chi = \mathbf{n} \cdot \mathbf{n}'$. In the limit of $J \gg 1$, the integral in Eq. (7) reduces to $d^2\delta(x)/dx^2$ evaluated at $x = m - J\mathbf{n} \cdot \mathbf{n}'$. Since m can be taken as a quasicontinuous variable, we integrate by parts to obtain

$$Q(J, \mathbf{n}) = \frac{2J+1}{4\pi^2} \int_{-\infty}^{\infty} dm \int_{\mathcal{S}_2} d\mathbf{n}' \frac{d^2 w_m^J(\mathbf{n})}{dm^2} \delta(m - J\mathbf{n} \cdot \mathbf{n}'). \tag{8}$$

Thus, in the limit of high photon numbers, the reconstruction turns out to be equivalent to an inverse Radon transform [20] of the measured tomograms, which greatly simplifies the numerical evaluation of $Q(J, \mathbf{n})$.

In Fig. 3 (top), we show the result of the three-dimensional inverse Radon transform for a polarization squeezed state. Here an isocontour surface of $Q(J, \mathbf{n})$ in the Poincaré space (that results from representing the average values of $\hat{\mathbf{J}}$ in a three-dimensional Euclidean space having J_1, J_2, and J_3 as orthogonal axes) is seen. The ellipsoidal shape of the state is clearly visible. The antisqueezed direction of the ellipsoid is dominated by excess noise stemming largely from photon-phonon interactions, which is characteristic of squeezed states generated in optical fibers.

In Fig. 3 (bottom), we compare the projections on the coordinate planes of the isocontour surfaces of a coherent and a polarization squeezed state for the value corresponding to the half maximum. The contours agree with the 6.2 ± 0.3 dB squeezing that was directly measured with a spectrum analyzer. The elliptical contour in the J_1-J_3

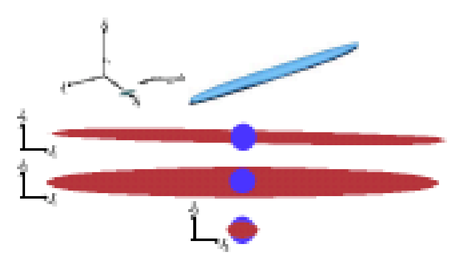


FIG. 3 (color online). Sections of the isocontour surface plots of the Q function for a coherent state (blue) and a polarization squeezed state (red).

(middle pages of first articles in current issues)

The difference between physics and biology is not just that physics “makes more use of quantitative methods” (although it does).

In physics, we are searching for an understanding of Nature that we can summarize in mathematical terms.

Mathematics is not an optional accessory, nor is it merely a tool alongside many others.

“La filosofia è scritta in questo grandissimo libro che continuamente ci sta aperto innanzi a gli occhi (io dico l'universo), ma non si può intendere se prima non s'impara a intender la lingua, e conoscer i caratteri, né quali è scritto. Egli è scritto in lingua matematica, e i caratteri sono triangoli, cerchi, ed altre figure geometriche, senza i quali mezi è impossibile a intenderne umanamente parola; senza questi è un aggirarsi vanamente per un'oscuro laberinto.”

~”The book of Nature is written in the language of mathematics.”

(Galileo Galilei, 1623)

Two related but distinct goals

Educate biologists who find it natural to do quantitative experiments, sophisticated analyses of their data, and meaningful comparisons with theory
(because biology is so big, even incremental progress can have a big impact)
(perhaps we shouldn't be shy to say "make biology more like physics")

Educate physicists who find it natural to bring the "physicist's style of thought" to study a broader class of systems, including biological systems
(this clearly can't be accomplished by learning less physics!)

These goals are very different at the graduate level.

Given the state of biology education today, meaningful progress on the first goal is hard to achieve if you wait until graduate school.

Similarly, if you wait too long to start work on the second goal one has to face large barriers of language and habit

So: start at the beginning!

Boundary conditions

First, do no harm.

For the first year, we want to create an alternative to the combination of freshman physics and chemistry ...

While we want lots of connections to biology, we don't want the responsibility of communicating the factual content of intro bio courses (save this for a sophomore follow up course).

All relevant departments need to agree that we have delivered the equivalent of freshman physics and chemistry (+ a little CS) at some level.

Thus, students from our course will have access to the full range of majors.

As in our physics courses for majors, we build on previous mathematical experience, but will teach some of what we need as we go along.

We simplify our problem by taking students who have had a calculus course at the level of AP Calculus BC.

You can't satisfy the boundary conditions without genuine collaboration among the departments.

In particular, a top down initiative won't work.

(... There's a man with a gun over there, telling me I got to beware ...)

We had the good fortune to have a group of faculty from all the relevant departments who were interested in rethinking freshman science education in the broadest sense. We worked from a "zero base budget."

Faculty

W Bialek (physics)
CG Callan (physics)
D Botstein (molecular biology)
B Chazelle (computer science)
JT Groves (chemistry)
M Hecht (chemistry)
L Hodges (teaching center)
L Kruglyak (evolutionary biology)
D Marlow (physics)
J Rabinowtiz (chemistry)
C Schutt (chemistry)
O Troyanskaya (computer science)
EF Wieschaus (molecular biology)

Lewis-Sigler fellows

M Dunham, E Pearlstein, WS Ryu & EM Schoetz (experimentalists)
M Desai & M Kaschube (theorists)

Plus ... <u>many</u> teaching assistants from all departments

Freshman physics topics

Newtonian mechanics

Electricity and magnetism (up to Maxwell)

Waves

Thermodynamics and a little statistical physics

(sometimes) “Modern physics”

Freshman chemistry topics

Thermodynamics and chemical equilibrium

Reaction kinetics

A tour of the periodic table

Chemical potential, electrochemistry, ...

Orbitals, bonds, ...

There are obvious commonalities, and some more subtle relationships through the common mathematical structures

Can we organize around these more general ideas?

What kinds of mathematical structures do we use in describing nature?

Functional relations

$V = IR$, $Q = CV$, $F = -kx$, $F = -\gamma v$, ...

Dynamical models (differential equations)

Elements of classical mechanics (more viscosity than usual!), chemical kinetics (including enzymes, approximations), ... stability and response in genetic switches, resonance in the cell membrane, ...

Probabilistic models

Boltzmann distribution, connections to thermodynamics (more complex examples, e.g. protein folding), but also genetics, ...

Fields

Electricity and magnetism, but also diffusion, ... pattern formation in development, ...

The quantum world

(example) Six weeks on probabilistic models

Genes, combinations and probability (with some inference)
Gas laws and the Boltzmann distribution
Brownian motion and the reality of molecules
*Emergence and approximation
Chemical equilibria and thermodynamics
Entropy, from Carnot to Shannon

$$\begin{aligned}
\langle E\rangle &= \frac{1}{Z}\sum_s E_s \exp(-\beta E_s) \\
&= \frac{1}{Z}\sum_s \left[-\frac{\partial}{\partial\beta}\exp(-\beta E_s)\right] \\
&= -\frac{1}{Z}\frac{\partial}{\partial\beta}\sum_s \exp(-\beta E_s) \\
&= -\frac{1}{Z}\frac{\partial}{\partial\beta}Z,
\end{aligned}$$

we aimed high: mathematical sophistication at the level of our honors freshman physics course

a. Suppose that we make one measurement of the velocity of a molecule and find the results $v_x = v_1$. What is the value of the temperature that is most likely to have generated this data point?

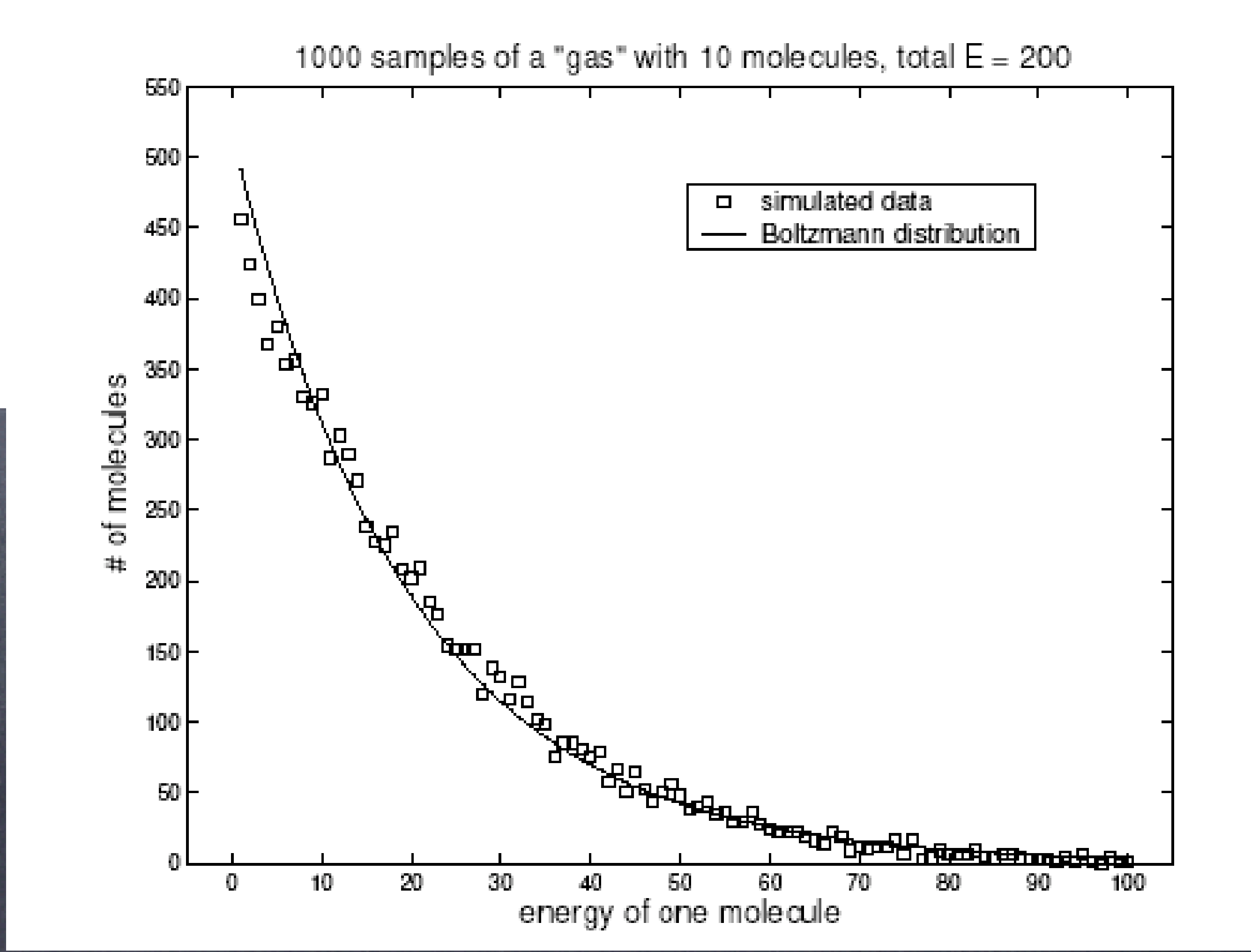
b. Let us make measurements on two molecules, with results v_1 and v_2. What is joint the probability distribution of v_1 *and* v_2? Generalize this to making n measurements.

c. Given n measurements $v_1, v_2, \cdots, v_n$, what is the value of the temperature that is most likely have generated this whole set of data?

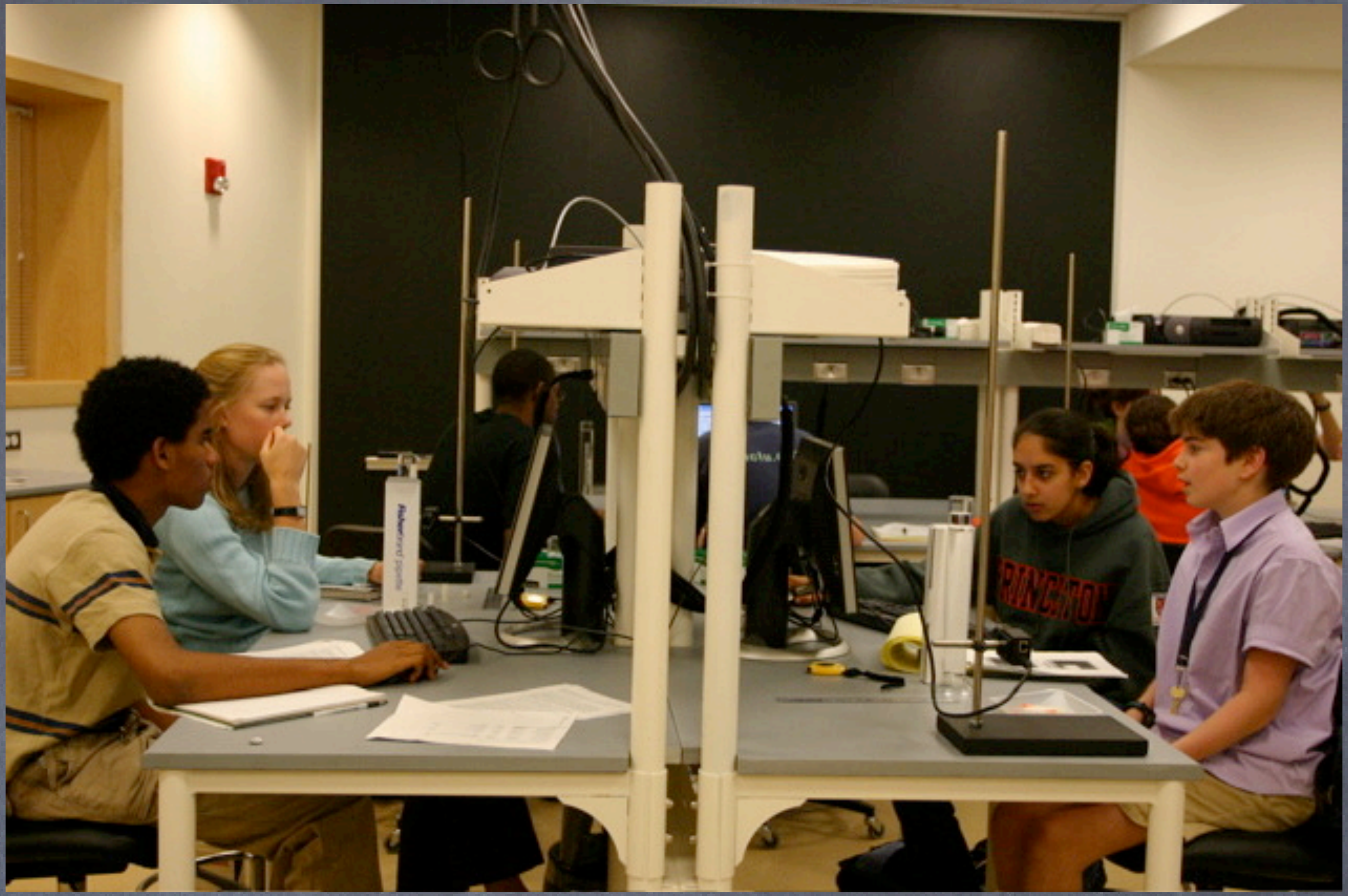
Getting some help from the computer:
Exploring the combinatorics that leads to the Boltzmann distribution

In MATLAB, we can let states be 1000 samples of a list of 10 numbers, so it is a 10 × 1000 array. To pick the energies we use rand, with a little trick to turn the continuous distribution into random integers from 1 to 100. We have to try many times in order to be sure that we will find 1000 examples that meet our criterion for the total energy.

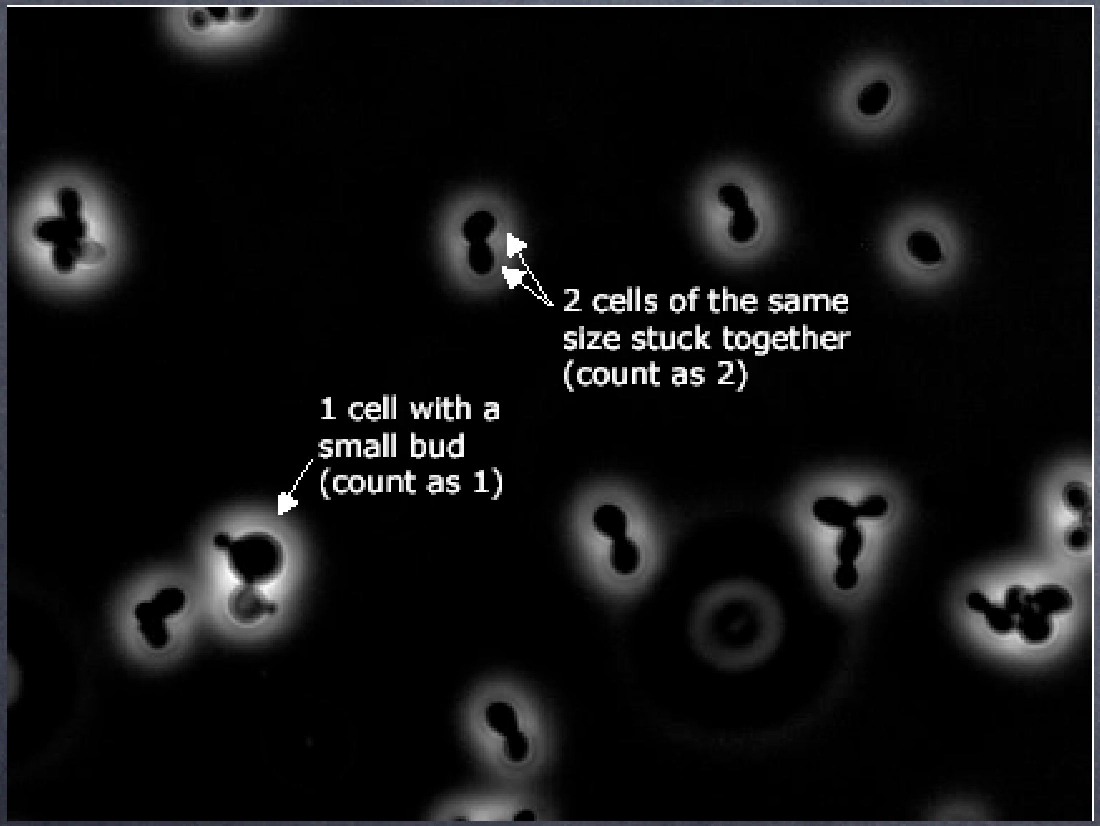
```
Nsamples = 1000;
states = zeros(10,Nsamples);
k =1;
for N = 1:1e8;
    if k <= Nsamples;
        s = ceil(100*rand(10,1));
        if sum(s)==200;
            states(:,k) = s;
            k = k+1;
        end;
    end;
end;
```



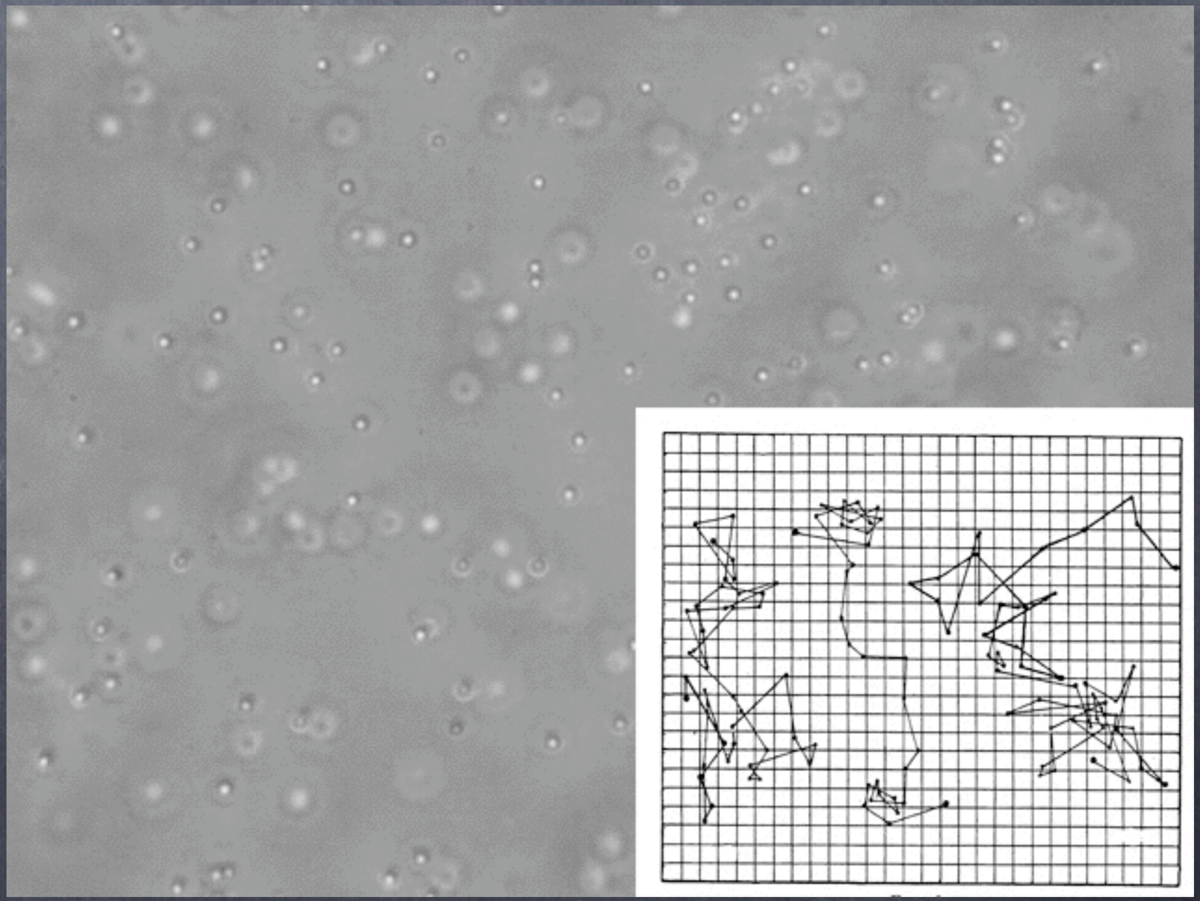
Meanwhile, in the lab ...



Delbrück-Luria experiment with yeast



we meet weekly to keep labs, lectures, problem sets, ... all tied together



Direct measurements of Brownian motion

The pioneers (now seniors)

and this is after the final exam

This year: 49 students in the freshman class
~1/3 of Juniors majoring in Physics came through our course
~1/2 of students so far major in Molecular Biology, instantly the "go to" people for quantitative analysis, changing what gets done in the labs