can alter traits without compromising fitness in the field will also be relevant for molecular crop breeding.

Why is Europe so critical of GMO crops? As long as it is cheaper to import food than to produce it locally, Western European countries have no need for GMO crops. Where it does matter is Africa. In my scientific opinion, GMO food is safe to eat, GMO crops can increase yield and, when used wisely, are good for the environment. Unfortunately, scientists are helpless in the emotional and politically charged debate. I sincerely hope that one day Greenpeace will conclude that GMOs are not just evil but might, just might, help save the lives of starving children. Greenpeace has great powers of persuasion, and with power comes responsibility.

If you could start again what would you like to work on? Of course, one of the great things of academia is that you can start something new any time, if you really want to. We visited Yellowstone Park last fall and those brilliant thermal pools reminded me how interesting cyanobacteria are. Four billion years ago, cyanobacteria were the dominant form of life — they invented oxygenic photosynthesis and changed the Earth. Today, they thrive in marginal habitats, or as chloroplasts, engulfed and enslaved by colorless proto-eukaryotes. I would like to do single-cell genome sequencing of cyanobacteria and other ancient bacteria from unusual habitats. I would look for enzymes with unusual substrates that had to be taken up from the environment. Such 'reverse ecology' would tell me something about the organic compounds present at the beginning of life. Potential building blocks of a pre-RNA genetic material would be particularly interesting. Cyanobacteria probably drove more ancient life forms to extinction. Or perhaps they didn't? If their genetic material is not PCR-amplifiable, if they are not abundant and grow slowly, nobody would have noticed them. It is hard to imagine the Swiss National Science Foundation funding such a project, but it is fun to think about it. And isn't wild speculation the raw material of science?

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Essay

Intellectual immigration

The influx of physicists to the realm of biology around 1940 represented the birth of molecular biology. Now, with the sequencing of thousands of genomes and the promise of the $1,000 human genome, we find ourselves returning to physics. The cell is a foreign place, one that requires concepts from physics and statistical mechanics to gain a basic understanding.

Kerry Bloom

Why should we care how long bacteria can swim without energy, or why you can run but not walk through muddy water? The answers to these questions reveal two basic biophysical processes. One is known as Reynolds number (a dimensionless number, the ratio of inertial/viscous force). In a highly viscous environment, mass is irrelevant, and upon loss of energy a bacterium will drift less than the width of a hydrogen atom. Second, non-Newtonian liquids such as muddy water exhibit properties of solids or liquids, depending on the frequency of sampling. The world without gravity (Figure 1, low Reynolds number [1]) is much more representative of life in a cell than our intuition leads. In fact, our intuition fails miserably when we scale down to cellular dimensions. Our world is dominated by inertia — air is our viscosity. The state of constant motion exhibited by all molecules (k_BT = 4.1 pN nm) is completely foreign as we consider our macroscopic world. It is critical that we entrain our intuition with the conditions and experiences encountered by those molecules we yearn to understand. The challenge for 'biologists' is to distrust our instincts, learn a new language, and embrace a world in which there is no gravity, everything is in constant motion and it is thick as molasses. Welcome to the world of the cell.

We turn to the providence of biophysics to provide a basic understanding of the world inside the cell. Let's start with a very simple relationship $\Delta G = \Delta H - T\Delta S$ (Gibbs free energy = Enthalpy – (Temp*Entropy)). In living cells temperature is constant (homeostasis). Thus, we need to look at the Gibbs free energy relation and ask where the sources of energy are. For living matter, the energy source is in enthalpy (ΔH) and the number of conformational states (ΔS). While insights from structural biology cannot be overstated, the number of conformational states and their contribution to biological processes is even more sobering. There are several simple essays that peer into the world of the cell. One is "Life at low Reynolds number" by E.M. Purcell [1]. Purcell describes life in a world dominated by viscosity (Figure 1). In this world, there is no coasting, nuts do not fall off bolts when unscrewed, and walls are not needed to confine biochemical reactions. Second, "There's plenty of room at the bottom" by R. Feynman [2], in which he explains why combustion engines don't work at small scales (heat is dissipated very quickly) and how much room there is at the molecular level. If you take the 'air' out of the atoms in our body, the remaining mass would fit on the head of a pin (*The Tao of Physics*, F. Capra [3]). It's easy to appreciate how our intuition fails in these situations — the challenge is to gain intuition that will guide our quest to understand the mysteries of life.

For a cell biologist, there is not one book that provides the biophysics underlying problems as diverse as the cytoskeleton, chromatin, protein sorting, signaling or nuclear organization (to name a few). Biophysics requires applied math, material science and engineering, physics, polymers, chemistry and biology. There are language and conceptual issues, including diffraction and quantum theory. The tools to tackle complex biological problems such as DNA sequencing, mass spectrometry, and sub-resolution light microscopy generate enormous data sets that bring quantitative and statistical challenges in analysis. In teaching transcription, we now include a discussion of noise and how noise can amplify signals in non-linear processes. In teaching chromosome segregation, we find papers that consider polymer repulsion and the

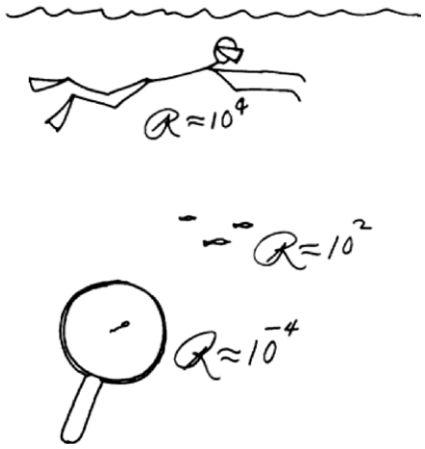

Figure 1. Reynolds numbers.
Reprinted with permission from Purcell E.M., Am. J. Phys. *45*, 3–11 (1977). Copyright 1977, American Association of Physics Teachers.

number of entropic states. We are in a brave new world that demands a new intuition.

The classic books provide an entrée into this world (*The New Science of Strong Materials and Structures*, and *Why Things Don't Fall Down* by J.E. Gordon [4,5]). Cellular material can be soft or hard, elastic or viscous. For a given structure (*e.g.* DNA or microtubules), one needs to know its material properties to understand the physical constraints that dictate its size, shape and stiffness. Stress and strain have specific mathematical meanings (stress is pressure, N/m^2; strain is length change, $\Delta L/L$) and help us understand what makes materials strong or weak inside a cell (Young's modulus = stress/strain). Biologists are fascinated by failure — the basic tool in genetics is to break it (mutation). In a wonderful description of glass making, J.E. Gordon reveals why thinner whiskers are stronger — as one approaches atomic width, fewer and fewer flaws are tolerated. *Giant Molecules, Here, There and Everywhere*, by A.Y. Grosberg and A.R. Khokhlov [6], was written by leading polymer physicists for high school students in Russia. It provides a deep understanding of polymers and their behavior in simple language. We learn about random and directed walks, polymer reptation, and properties of a cross-linked network. *Giant Molecules* provides insights into the organization of the chromatin polymer, long chain polysaccharides, and liquid crystals that cannot be gained from biochemistry.

Major physical concepts that need to be integrated into the lexicon of a cell biologist

Molecular dynamics

Thermal motion is vibrant and the one number to know is 4.1 pN nm (K_BT) [7]. This is the natural motion characteristic of every molecule and atom in the cell. Nothing is static — in contrast, it is rather violent in the cell. Brownian motion is the engine for diffusion. An analogy for diffusion in our world is popping a helium balloon, or for the kinesthetic learners, releasing kindergartners on the playground. Efforts to illustrate the violence of this motion include an exciting collaboration between a biophysicist and artist (D. Odde and C. Flink [8]). Large structures whose diffusion may be 'slow' are nonetheless in a constant state of motion. For biologists, this shows us that looking at individual events is dangerous. In a world of constant motion, we must take many, many snapshots to capture the range of events. Luckily, this is the bailiwick of physicists, and is called statistical mechanics, whereby we can extrapolate the behavior of individual molecules to a probability function and deduce the properties of the whole. Statistical mechanics may inform long-range correlations beyond individual interactions (*Biophysics: Searching for Principles*, W. Bialek [9]). The operative word here is *probability*. By looking at the distribution of a population, measuring its variance, examining correlation and cross-correlation, we can infer much about the physical properties of the structure. The law of equipartition of energy says that the variation in position (σ) of an object is related to stiffness (equipartition theorem, $K_s = K_BT/\sigma^2$). We can use this equation to calculate stiffness, spring constants, and binding energies in living cells.

Noise

As soon as we start amassing large data sets, we encounter noise. For instance, is the variation we see in experiments due to noise or reflective of the equipartition theorem? In *Biophysics,* W. Bialek notes that biologists like to inform physicists that their data are inherently noisy. However, computer scientists know that noise can amplify small signals, a process known as stochastic resonance. It is most likely the case that biology exploits this process. If a system is completely linear, noise cannot benefit detection; however, in a non-linear system (such as threshold) noise can produce an overall beneficial (more sensitive) effect. The challenge for biologists is to be as precise as physicists in their measurements, recognizing that we need to deconvolve data into signal and noise, respectively. Acknowledging that living systems are intrinsically noisy, the question becomes whether cells use noise to make decisions. The combination of noise and non-linear processes has been shown to amplify signals in chemical sensing, create oscillations in cell signaling, and generate patterns in gene transcription. In an analogy with a child's mobile, Springer and Paulsson [10] discuss how oscillations can be driven by noise. Alternatively, there are mechanisms of noise reduction, such as kinetic proofreading — balancing the energy cost of accuracy by introducing an irreversible transition into the reaction mechanism. As analytical and statistical methods improve, an emergent paradigm is that optimal efficiency is attained by simply tickling the thermodynamics of the systems. Cells have evolved to operate right at their physical limits of synthesis, degradation and recognition. As cell biologists, we need to have a deep understanding of these physical limitations and their dynamic properties to begin to understand basic cellular mechanisms.

Polymer dynamics

One of the big unanswered questions in chromosome biology is the packaging problem (Figure 2). While the genetic code is currently enjoying its time in the limelight, we are making incremental advances in packaging. From the mechanical perspective, DNA is an entropic spring — the polymer will adopt a random coil in order to maximize the number of entropic states [6,11]. Whenever a polymerase, topoisomerase or microtubule (using the kinetochore), applies an extensible force, entropy will drive the helix back to a random coil. This is conformational entropy, and the number of states that a long chain polymer can adopt is exceedingly high. How forces are transmitted, how action on one segment (gene) influences another is the realm of polymer physics. The size of a polymer

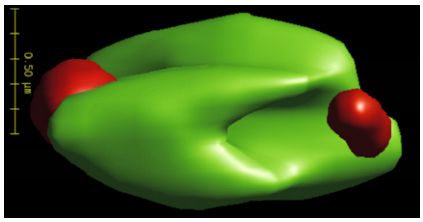

Figure 2. A practical application.
A macromolecular assembly of cohesin (green) packages DNA (not shown) and encircles the spindle apparatus (poles in red) in budding yeast.

coil is dictated by the number of segments (contour length Lc) and the length of each segment (persistence length Lp). The size of the coil is at least ten times the size of the nucleus it is packaged within. Packaging DNA, whether in a virus capsid or a nucleus, is an energy-consuming process, and upon relaxation, entropy and the stored energy will drive the DNA to expand. The consequence of confinement has inspired several investigators to explore whether polymer repulsion in small spaces can contribute to mechanisms of bacterial chromosome segregation [12].

Non-Newtonian fluids

Living in air and swimming in water does not help us appreciate life in a tar pit (viscoelastic polymer). In addition, our cellular tar pit exhibits different properties depending on the speed of sampling (frequency). Fast-moving objects encounter a solid, whereas slow-moving objects encounter a liquid. To understand the dynamics of our favorite structure we need to know the size as well as time scale of motion of the object. Several renown mathematicians have developed algorithms to deconvolve the viscous (shear loss) and elastic (shear storage) modulus from the motion of an object in solution (mean square displacement) [13,14]. These data provide the biologist a measure of the fluid properties in a frequency domain relevant to the process under study. Cellular structures are jostled, shoved, and just about every other insult you can imagine stuffed in a crowded New York subway. Deducing the loss and storage moduli is essential for understanding how the network contributes to the motion of a structure. This is where biologists need to challenge (or become) physicists to develop quantitative methods for ferreting out basic principles hidden in complex behaviors.

Mechanical signaling

Forces acting on a target at the cellular or molecular level result in deformations that convey information. There are critical differences between chemical vs. mechanical signaling. Firstly, force is a vector and thus mechanical signaling has direction, in contrast to diffusion of a chemical reactant. Secondly, mechanical signals can be generated quickly and transmitted instantaneously over long distances. Thirdly, mechanical signals quantified as strain (see above) decay, or dissipate, linearly (1/r) while chemical signals in 2D decay as $1/r^2$). We are just starting to measure mechanical properties of cells and finding significant differences throughout development and disease.

Computer vision and modeling

For physicists, mathematicians and computer sciences, building toy models to simulate a process is an integral part of their toolbox. Biologists are just starting to complete the parts list, count molecules and measure kinetic parameters to make testable models. A model should be considered as a tool to guide our intuition in this strange world of the cell. The challenge is to translate the model prediction into the form of experimental outcome. One method, model convolution, does just that [15]. By convolving points in space with the point spread function of a microscope objective, Odde and colleagues [15] have developed methods to present model predictions in the precise form of experimental data. In this way, parameters can be adjusted and simulations can be generated for evaluation by the experimentalist. Another major approach is to exploit the processing ability of a computer to analyze enormous data sets. Our abilities to deduce principle components of a system are no longer constrained by its complexity. We have broken the negative correspondence between complexity and understanding with computer vision [16]. These computer-intensive approaches coupled with the knowledge of the physical properties of our specimen and its environment will provide us new intuition that will serve as a guide for a deeper understanding of cellular function.

Searching for principles (*Biophysics*, W. Bialek) lays out the next challenge in cell biology. The 'bucket biochemistry' approach to deduce reaction mechanism got us the building blocks and basic wiring diagram. We need to step back and remind ourselves how noisy, crowded, and unpolluted the cell is. With amazing efficiency, the cell is the ultimate recycler and works very close to its physical limits as to accomplish tasks with minimal exertion. Noise can be friendly, information is a probability distribution and entropy can be useful. In *Biophysics,* W. Bialek uses these basic principles to build a search algorithm for navigating the cell.

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