Harness the Hubris: Useful Things Physicists Could Do in Biology

We tell ourselves that biologists need physicists and that biological materials present a big opportunity for physics, but then physicists and biologists don't train themselves to work together and learn from each other.

V. Adrian Parsegian

I once asked my father why he chose physics when he started at MIT. "Everybody said it was the hardest course, so I decided to do it."

It goes through all of physics, I think, the idea that not just anybody can do it and that when you've done it you can do anything—cook, repair cars, analyze stocks—and certainly give an occasional gift of superior attention to matters biological.

Biologists aren't so sure. The bad jokes are a tip-off.

Physicist: "I want to study the brain. Tell me something helpful."

Neuroscientist: "Well, first of all, the brain has two sides."

Physicist: "Stop! You've told me too much!"

And yet so many big advances in biology and medicine are by-products of good physics—for example, all that scanning at the hospital and all that x-ray and neutron diffraction giving molecular structures. Physicists are already doing useful things for biology, whether biologists and others realize it or not.

Not that there is anything wrong with nominally useless physics. I prefer it, and I recommend it. We know why we choose "useless" problems. They allow us to do our best learning or our best-quality work. We can have the big ideas and think new concepts in language that is appropriate to physics. Good basic physics, in biology as elsewhere, carries its own justification. Sooner or later it pays off in the biggest ways.

Still, the information gathered through molecular biology creates huge opportunities and needs. Mapping entire genomes is only a first step; the next steps require thinking about all those data and the structures that go with them. The amount of information invites grand comparisons: Ten voyages of the *Beagle*? A hundred Lewis and Clark expeditions? A thousand Kepler notebooks?

"You guys are going to inherit the Earth," an associate director of the National Cancer Institute remarked to me, talking about how physicists and chemists are going to be there to work with all this information. Certainly NIH is interested in physics initiatives. And, conversely, condensed matter physicists are seeing value in their proximity to biologists.

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In large areas of biology, good physics is desperately needed, although surprisingly few physicists seem to realize it or want to do something about it. This article is not a list of research projects, though it would be easy to turn out such a list. Rather, I outline three general areas in which physicists can contribute to biology. Some of my examples are intentionally autobiographical. (It would be good to learn of more opportunities from the experiences of others.) Physicists can

▷ Teach physics—elementary physics—to people in other subjects; there's a need and, presented at the right time, a hungry audience. Awareness of physics is dying. This trend is not just evident in the drop in the number of students entering and then practicing physics; it is even clearer in modern biology, where physics is being shrugged off just when it can be most useful.

▷ Choose materials whose naturally selected biological properties are properties that we learn to handle as physicists. There are relatively neglected but large classes of biomaterials that physicists might be able to study better than could other kinds of scientists.

▷ Use physics on systems about which too little physics is known. Good physics can explain the biological properties of many systems. Molecular forces and dynamics, for example, areas of prime strength for physicists, are still applied to biomolecules in crude ways.

Teach physics

When I was editor of the *Biophysical Journal* several years ago, I used to enjoy reading all the submitted manuscripts as a kind of free education. Some time into my editorial stint, it began to dawn on me that most "biophysical" authors were crippled by knowing very little physics. A friend and I once joked that there should be a qualifying exam to join the Biophysical Society: Ask people to solve a quadratic equation. It's not surprising that many of the real physicists working with biomaterials label themselves "biological physicists" and prefer to go to American Physical Society rather than Biophysical Society meetings.

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FIGURE 1. TEACHING PHYSICS: an optics tutorial for biologists at the National Institutes of Health. (Photo courtesy of Leslie Barden, NIH.)

One of the best biophysicists I know, deservedly respected for the combination of theory and experiment in his work, once told me, "All the theory I know is Coulomb's law." That was in response to a suggestion I had made for another way to look at his data. After I made another try, he said, "Adrian, all the theory I will ever know is Coulomb's law."

Worrying about curriculum and the pressures of teaching so much new molecular biology, people wonder what old subjects to drop. Physics is usually high on the victim list. I remember an essay by James Watson on science training that said early on, "I'd skip the physics"—he with his prize built on x-ray data.

Some years after editing the *Biophysical Journal*, I took a sabbatical at Princeton University, back to a physics department for the first time since graduate school. I wondered what kind of physics the bio-destined students were getting. At the middle of the year, I cotaught the second term of their elementary physics course. On the first day I asked, "For how many of you is this your first physics course?" All hands went up, reluctantly. "For how many of you is this your *last* physics course?" All hands flew up, forcefully.

I think we enjoyed each other, the students and I. It was fun teaching the old-time religion—the Bohr atom, special relativity, very elementary circuits—but I'm sure what those refractory captives heard did them little good. In their salty lab preparations, even electric potentials differed from the concepts we were teaching them.

At our beloved National Institutes of Health, most scientists were once the kind of bright kids I met at Princeton. Most of them don't know physics and its applications to their problems, but a surprising number wish they did. I'm amazed at how many people turn out for a course on practical, user-friendly physics. I'm told there is a fear of numbers and math, but people will overcome fears when they feel the need.

College physics courses have been developed for biology majors. Some of the texts I've seen are quite attractive. But as far as I can tell, these courses remain relevant only to important realities such as medical school entrance exams.

We need courses in simple physics. It wouldn't hurt doctors to get a year of biological physics in medical school, to at least learn enough to know how their hospital apparatus works. The same holds for lab scientists. (Yes, I know the dumb line, "You don't need to know how a car works to drive it." That argument doesn't work here. You'd better know what that machine actually does if you're going to use what it tells you.)

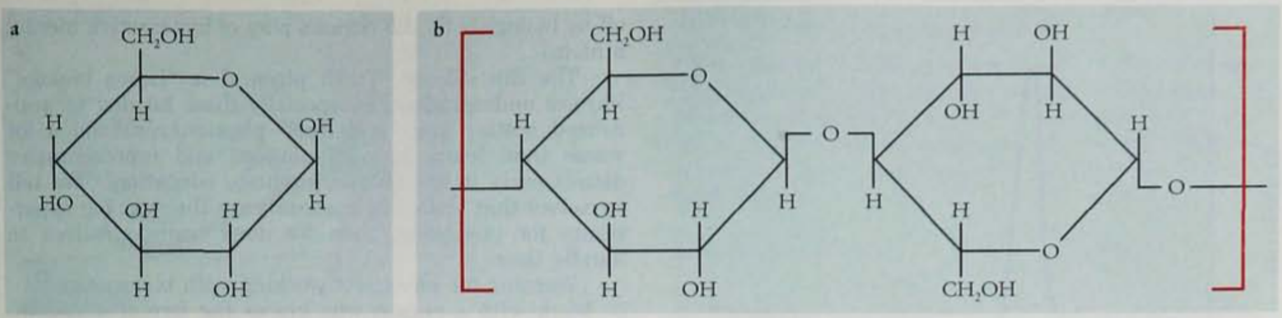
Most of this learning probably has to come after graduate and medical school (see figure 1 for one example), although pertinent physics taught to undergraduates or graduate students would go a long way toward opening dialog and lessening fears. It is more practical to think of continuing education when one perceives the need to know how a particular protein works or how a cell surface receptor can hold and use its "agonist."

Basic means basic: physics 001 revisited without fear and without ego stuffing by physicists showing off how they idealize real molecules into analytically convenient symmetry.

Even within physics, I see an important death. Thermodynamics, essential to so much thinking in biology, is a dying language. It is still spoken in some areas of physics, but even there more for cataloging than as the living language it was created to be. (You want to unnerve a hotshot theorist? Ask him to explain the difference between a partial and a total derivative of a thermodynamic state function.) They say a church is only

Hierarchy of Information

Class	Use	Amount
Nucleic acids	Genetic code Transcription Translation	Very small numbers of DNA—for example, two copies of DNA per cell Multiple copies of RNAs Negligible secretion
Proteins	Regulation Catalysis Structure	Huge number of kinds, relatively few copies of each kind Largest part of cell mass A few species massively secreted
Lipids	Compartmentalization Insulation Scaffolding	Aggregates, many copies of relatively few types compared to proteins
Polysaccharides	Structure Energy storage Solution properties; viscosity	High copy number Much storage in cells Large amounts secreted



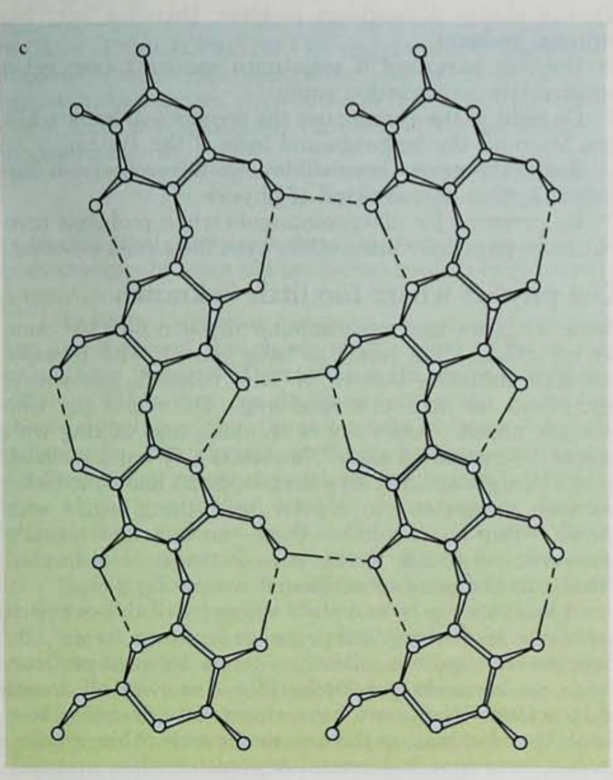


FIGURE 2. BIOPOLYMERIZATION. Soluble glucose (**a**) can be connected by flexible single bonds to form β-linked "polyglucose" (**b** and **c**). This most common natural polymer is cellulose, whose solubility is negligible because of the intricate fit of hydrogen bonds between hydroxyl (-OH) groups. The details of this fit are essential to the biological and physical properties seen in nature. (Part **c** from R. H. Marchessault, P. R. Sundararajan, in *The Polysaccharides*, vol. 2, G. O. Aspinall, ed., Academic, Orlando, Fla., 1983.)

one generation from extinction. How about a subject that is not seriously taught? Somebody has to keep thinking carefully about heat, work and energy. If not, these concepts will have to be rediscovered by biologists already baffled by the chemistry of bioenergetics. Maybe in addition to the suggestion "Teach physics," we should say "Remember physics" or "Preserve physics."

Choose new materials

Thinking about physics in biology, I was struck a few years ago by the comparative neglect of whole classes of materials. In particular, I was newly aware of the polysaccharides, on which two of us had just been able to make intermolecular force measurements. We sent the paper to *Science*, which accepted it—but as a technique paper, not because intermolecular forces between polysaccharides were in themselves interesting.

What occurred to me soon after our *Science* article appeared was that the properties for which polysaccharides are created in nature are often physical properties—controlled viscosity, lubrication and strength, as well as energy storage. I began to compare the different classes of biomaterials—the properties for which they are used in living systems versus the properties about which physicists are trained to think. The neglect of polysaccharides by physicists became even more puzzling. God clearly invented those molecules for physicists.

In my mind, I made a chart listing four major categories of biomatter, ordered in the hierarchy of information that they contain for molecular and developmental biology. (See the table on page 24.) Next to each category I put its biological functions. A third column noted for each class the amounts of material found in nature—or, perhaps better, the numbers of each kind of molecule. Compared to lipids and polysaccharides, nucleic acids are a small part of the biomass. Proteins, which as a class receive the most attention, are most of the mass of most cells. The number of different proteins is vast, but, except for the structural proteins, they usually come in relatively few copies, according to their specific tasks. There are fewer kinds of lipids, but those molecules occur in aggregates of thousands. Proteins, lipids and polysaccharides can be secreted or extruded for quantitative use; nucleic acids cannot.

My chart is necessarily an inadequate simplification of properties, and I'm sure anyone can find favorite gross inaccuracies. But there is here, it seems to me, a basis for seeing why different kinds of training can lead people to choose differently in dealing with these classes of materials. Molecular and developmental biologists gravitate toward those components critical for genetic and developmental regulation, components that occur in relatively small copy numbers. Physicists might go for long molecules produced in large quantity for their physical properties.

To me, the chart suggests two different sequences of interests:

▷ Biologists: nucleic acids>proteins>lipids>polysaccharides
▷ Physicists: polysaccharides>lipids>proteins>nucleic acids

It has worked out that way for biologists, but not for physicists. There are lots of good, overlooked physics problems.

But one must be careful. In biology, details matter. For example: The sugar you stir into your coffee is sucrose, made of two smaller sugars, one of which is glucose (figure 2a). Think about a long string of these glucose molecules hooked together by flexible single (β) bonds (figure 2b). This is cellulose, boringly described as the most abundant biopolymer on Earth.

Is it any problem to dissolve this polymer of loosely linked glucose? In fact, these molecules fit together quite differently from what one might expect. There is an

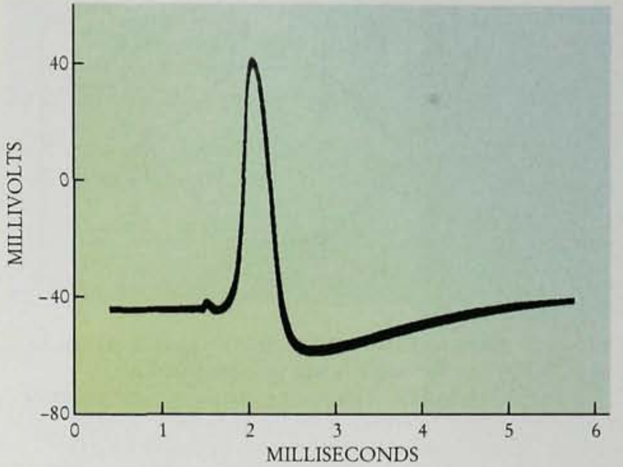


FIGURE 3. 'ACTION POTENTIAL' of a signal-conducting nerve axon. The successive rise, drop, overshoot and recovery of the voltage as a function of time is precisely controlled by the combined action of several different proteins, whose characteristic voltage-response times differ by milliseconds. How does nature create different millisecond timescales for the conformational changes of its macromolecules? How will theorists model these times with simulations that cover only nanosecond intervals? (Trace from K. S. Cole, *Membranes, Ions and Impulses*, U. California P., Berkeley, 1968.)

intricate matchup that holds neighbors tightly together (figure 2c). Putting that lump in your coffee would be as futile as trying to dissolve sawdust. (No point anyway; we can't even digest it.) Another flexible single (α) glucose linkage creates soluble starch (easily digested).

Any beads-on-a-string picture of the polymer would miss the point with cellulose. Such a witty idealization is immediately outsmarted by the dumbest of biopolymers.

"Physicists think language is beneath them, but they really must learn biology." That from my friend Donald Rau, a physical biochemist who turned down a sweet offer to leave us for another lab. "Somebody's got to make sure you physicists don't run off the track."

And yet there is almost a binary logic to the design of biological systems. To first approximation, a gene works or doesn't (though, more generally, different versions may work in different ways). A mutation triumphs or doesn't. A vast amount of memorization, messy chemistry and acronyms go into a linking logic that sometimes seems to be a simple puzzle game.

Terminology doesn't help. A biologist friend of mine was derided by a group of physicists when he said he used "interferometry" for measuring interference between nerve cells. After gasps and giggles about bad language and bad physics, physicists should begin to respect the molecular biologists for the tools they have created and the rules devised to guide their thinking.

Worse, cells themselves don't do physics the way we might do it. Think of the hopeless tangle DNA would have been inside the nucleus—two meters of string stuffed into a micrometer capsule—if it had been left as a physics problem. Instead, the cell cuts through all the knots and tangles using enzymes that make DNA, topologically, a phantom polymer that can cross itself. By creating spools and spindles (chromatin), the cell holds DNA in place for reading.

It's no wonder you can hear, "Biologists don't know physics, don't think physics." They don't think that physics addresses the specifics of their system. It's no wonder that much of "biologically inspired physics" is shrugged off by biologists as the curious play of hyperactive mental athletes.

The flip side of "Teach physics" is "Learn biology." Physics undergraduates, especially those headed for condensed matter and "materials" physics, could do a lot worse than learn biomanipulations and representative details early in their undergraduate education. We tell ourselves that biological materials are the next big opportunity for physicists, then we don't train ourselves to handle them.

Warning for physicists working with biologists:

▷ Work with a person who knows the lore of a system. There's always a language problem; there's a very big cultural problem.

▷ Don't be surprised if sometimes you can't even get a constructive conversation going.

▷ Go right to the system; use the physics you know while you learn all the language and logic of the system.

▷ Resist the nearly irresistible urge to reconceive a biological system as your kind of physics.

▷ Be prepared for disappointments when problems turn out to be physically intractable, even for a good physicist.

Use physics where too little is known

Some 25 years ago, my computer division director came by my office. "I'm ready to back you up with a major research initiative"—three or four postdocs, computing equipment for molecular modeling. He was a guy who saw far ahead. After lots of thinking and talking with people I respected, I said, "No thanks." What I realized, once I thought about it, was that we didn't know the forces between molecules. In physics, everything begins with forces. But no one knew them—no one had actually measured what the forces were between biomolecules. What was the point of additional computing power?

I was lucky to be in a place where I was able to switch my mode of working and learn to measure forces. By now, we have quite a collection—forces between proteins, lipids, nucleic acids, polysaccharides—involving all classes of biomatter. New laws have emerged to describe those forces that dominate at the nanometer scale of bioparticles. In fact, over that last crucial nanometer when mutually approaching molecules get serious with each other, measured forces look nothing like what was expected from micrometer-sized colloids or angstrom-scale atoms.

Still, as we speak:

▷ There is not one computer program that either predicts or even incorporates measured forces; there is no algorithm calibrated against what we now know to be the forces between molecules.

▷ Tens of millions of dollars are being used to design drugs "rationally" by computers using programs with idealized interactions.

▷ Heavy thinking about molecular assembly and folding rests on disproven assumptions about the operative forces.

Now that forces are being measured, systematic physical thinking is needed to codify, explain and apply them to the peculiar class of materials that work by them. We still need the equivalent of Coulomb's law for macromolecular interaction.

Once you crack the nanometer barrier, you see forces, dynamics and mechanics—often excitingly unlike their atomic or colloidal or macroscopic analogs. Still, their idiosyncrasies can be countenanced and described in classical physical language. On this size scale there is even a clear and new link between physical work and reaction chemistry. How does the work of ATP hydrolysis couple to proteins to create physical force? Buried inside all the cartoons and chemistry of bioenergetics is a "then-comes-a-miracle" step from chemical energy to physical force.

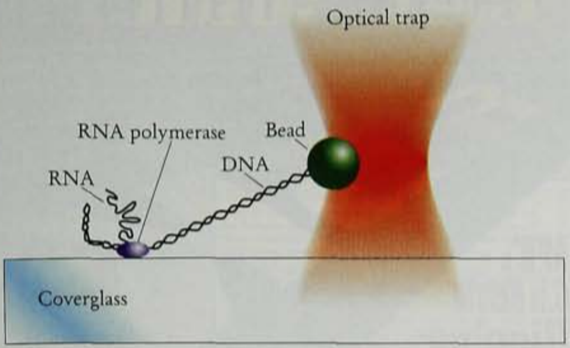


FIGURE 4. OPTICAL TWEEZERS for studying the mechanical properties of an RNA polymerase reaction. In this and in many related techniques, physical mechanics can be used at the level of single macromolecules. (Courtesy of Stephen Block, Princeton University.)

Systematic analysis is removing this miracle, reducing it to an example of some old statistical ideas brought down to the right size.

Like forces, molecular dynamics is a natural for physicists and a subject that needs serious work. One of the outstanding features of proteins is the variety of timescales on which they are designed to operate. Consider a nerve signal; note that the tick marks in figure 3 denote milliseconds. The electric profile comes from a sequence of different ionic channels working at distinctly different rates. How is a protein built to create precise characteristic times such as in the different times of ionic channels in nerves? Good physical theory can do a lot here. In a good week, computer simulation covers about a nanosecond of a protein's life. Even if we had the forces right, we would be a factor of a million too short in talking about functionally significant events. Brute simulation alone is unlikely to satisfy that factor anytime soon.

Progress in the mechanics of single molecules and membranes is much more encouraging and inviting. It is almost conception shock to witness the grabbing and stretching of single molecules of DNA during optical tweezer measurements (figure 4). It's near miraculous that the bending and stretching of bilayer sheets a few nanometers thick can be treated in the language of classical continuum mechanics. This is a time when the language of elasticity and mechanics is becoming part of the way we talk about many biological processes such as antigen/antibody binding, muscle tension, ion-channel conduction and cellular secretion. When you think of the powerful influence physicists have had on the "protein folding" problem using simplistic models, you wonder what good they would do with better physics on proteins or on simpler molecules.

Gentle suggestion

Real physicists may choose to ignore everything said here. I'm sure they know what they want to do and don't need to be told, as Robert Austin makes perfectly clear in the box at the right. I am only suggesting gently that there are unrecognized needs and possibilities for doing real physics working closely with biologists.

I have based this article on a talk I gave at Rutgers University on 16 December 1996. Helpful discussions with Sergey Bezrukov, Michael Edidin, Levi Gheber, Sergey Leikin, Valerie Parsegian, Peter Rand, Donald Rau and Helmut Strey have added to the pleasure of writing the article. ■

Counterpoint

To illustrate a different point of view and to stimulate debate, I have asked PHYSICS TODAY to include here the comments of its external reviewer. I thank Robert Austin for relinquishing his anonymity and allowing publication of his response to my article. Below his comments I give a brief response.

Dear PHYSICS TODAY,

I was charmed by Adrian's style of writing and amused by his entrance requirement for the Biophysical Society. But, now that I have been able to find the time to take a break from all the turmoil in the lab and think about what he has to say, I think this article sends exactly the wrong message to physicists.

What's wrong? In fact, the title says it all: "Harness the Hubris: Useful Things Physicists Could Do in Biology." In other words: You arrogant physicists! Don't even think about solving any big problems in biology like you have done in so many other fields! Know your place in the New Order! The best you can hope for is to provide some useful technical tools for the biologists.

I completely disagree with Adrian. Having lived with biologists and biochemists for a number of years, I know damn well that many of them can't reason their way out of a paper bag, and that they really need the analytical and experimental gifts of good physicists to help in the really major conceptual logjams that are facing modern biology. It may be hubris, but the fact is that some physicists are scary smart. Here at Princeton, I think some of the biologists recognize this fact, and are indeed turning more and more to brilliant physicists like Stan Leibler and John Hopfield to help wrestle with the really big questions.

Adrian's article is basically a capitulation; the three big things we can do are: teach good service courses, find good biomaterials and help biologists use good force fields. Forget that! I want to do the big problems: I want to understand energy flow in biomolecules; I want to understand how genes are turned on and off; I want to understand the collective processes in cell growth; I want to understand the immune system; I want to understand how the brain works; I want to understand the origins of consciousness. Don't tell me that I should be a good little boy and work on sugars first. No way! I'd rather drive a truck.

Adrian's article really is a recipe for defeat. What I think you should do is publish this as a two-sided article: Adrian with his timidity, and let a good strong physicist (not me!) write a reply that states the case for physicists at the very forefront of biology, working with the biologists on the biggest problems they can find. No appeasement! It isn't over until the fat lady sings, Adrian.

Firmly,
Robert H. Austin
Professor of Physics
Princeton University

As Bob well knows, most physicists don't work on the "big problems" even in traditional physics. Why are the "biggies" the only thing for physicists in biology?

Biologists have proven they are much more than stamp collectors. But don't underestimate collecting. While Bob's biologists and biochemists may be jammed in paper bags cataloging, they're scary smart catalogers without whose gift we would not even see the big problems. It hasn't begun until the fat catalog's read, Bob.

Patiently,
Adrian