Teaching Biological Physics

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As the field of Biological Physics expands at breakneck speed within our community and within our departments, the need for both undergraduate and graduate courses grows along with it. Such courses serve not only physics majors, but also students from the life sciences who need to understand the role of physical principles and concepts in understanding the world of biology. Using examples from three universities, we offer some perspectives on the justifications for departments to move into this area and incorporate biological physics into the standard curriculum, an emerging consensus on the syllabus for introductory and intermediate lecture courses for majors and non-majors in science and engineering, and an example of an advanced interdisciplinary graduate laboratory.

PACS numbers:

The past few years have seen an unprecedented surge of interest in biological problems by people with physics training, working in Physics departments. A host of new experimental and theoretical techniques has opened up the quantitative study of systems ranging from single molecules to vast networks of simple agents performing complex collective tasks. Many departments have begun aggressive programs to hire faculty into an emerging field called "Biological Physics." Engineering departments, too, are investing in the life-science/physical science interface, both in Bioengineering proper and in related areas, such as Chemical Engineering, Solid Mechanics, and Materials.

Not surprisingly, these new faculty (and often their colleagues as well) are interested in teaching the subjects that excite them. At the same time, physical-science students are beginning to demand courses relevant to life science, and high-level reports are emerging stressing the importance of quantitative, physics-based thinking for future life scientists [1,2].

With all this momentum, it may come as a surprise to find that many people, particularly junior faculty, tell us how difficult they have found it to create and sustain new courses in Biological Physics. We would like to examine some of the reasons for these barriers, and offer a few ideas for these courses that we have gleaned from our own and our friends' experiences.

It matters

The stakes are high. Most Physics departments feel that they must struggle to maintain their student enrollments. It often seems that scientifically talented students come to our universities already convinced that their best career options lie in the life sciences. That perception can be frustrating — after all, we know that many exciting advances in molecular and cell biology rest upon physical techniques and ideas. Why don't our students see this and study more physics?

Perhaps it is because when our students read course catalogs, they often get no hint of the great ferment going on in our laboratories. Many physics departments teach a collection of undergraduate courses whose outlines are similar to the corresponding menu of thirty years ago, despite the fact that the research interests of physics faculty have changed dramatically. The curriculum must change. In particular, we believe that Biological Physics must become a mainstream course in all Physics departments, offered as regularly as, for example, the current courses on solid-state or high-energy physics. We argue that it should be similarly emphasized in many Engineering programs.

Many departments already offer special-topics courses, graduate courses, and seminars in subjects relating to Biological Physics. As satisfying as this is, such courses often lack the stability enjoyed by the Modern Physics course, for example. They are frequently electives, which our busy students can't fit into their already crowded schedules. They are often limited in scope, unlike the overviews of a subject that we provide in condensed matter or particle physics. They frequently evaporate when a particular faculty member goes on sabbatical or is needed to teach a more "critical" course. Moreover, they are frequently created from scratch by junior faculty, who are already heavily burdened.

We believe it is important to offer a consistent, standardized course that is a requirement for at least some flavors of the Physics degree (and perhaps Bioengineering). An intermediate-level course can also be planned in a way that makes it a good candidate to be a recommended elective for other Engineering majors, as well as Biochemistry, and even Chemistry. Ideas for such a course are described below; it can serve a dual purpose if offered with a graduate-level section. As in our other intermediate-level courses, students in Biological Physics have much to learn from a hands-on laboratory, and we describe some of our experiences implementing labs at various levels.

Many of the concepts central to Biological Physics can also be taught at a lower level, and hence as larger service courses. A recent National Academy of Sciences report urges biology departments to begin requiring rigorous, and relevant, physics experience [1]. Premedical students, too, are frequently poorly served by our traditional MCAT-based courses. We will describe some ideas for meeting these challenges. Finally, many readers of *Physics Today* now teach in Engineering departments; we outline some experiences teaching Biological Physics in that context.

Looking beyond individual courses, now is also a good time to consider offering an entire degree program in Biological Physics, or at least a specialized concentration in the Physics major. Another recent article discusses ideas along these lines [3].

Seven reasons not to teach Biological Physics

Surely many of the our assertions above are not very controversial. So why do many faculty find obstacles in the way to creating courses of the type envisioned here? We hear faculty say that their colleagues offer objections of the following types.

"We don't have enough manpower; we're barely able to teach a complete curriculum of the old stuff." It's true. Physics departments have shrunk relative to the halcyon days of yore, forcing us to eliminate many advanced courses we think are important for our students. The only answer is that we must relentlessly prune our offerings to make room for the new, exciting subjects. Do we really need a two-semester sequence in X, when one might do? Do we really need to offer Y every year? Does the enrollment in Z really justify its existence as a regular course, or could it be offered as a reading course? All of these questions amount to: Would we really rather retain X, Y, and Z and miss out on Biological Physics? These aren't easy questions, but they do admit rational discussion.

"We can't justify a new elective course for our few majors." This question overlaps the preceding one. Here we will only suggest that the small number of physics majors may in part result from lack of curriculum options that students can imagine as relevant to their own future careers. What's more, we find that Biological Physics attracts students from several other majors, not just a captive audience of the few Physics majors.

"It's already offered in another department." It's true that other departments offer courses with names like Molecular Biophysics, Physiology, Medical Imaging, Neuroscience, and so on. On closer inspection, however, we often find that the material our students need is thinly distributed through many different courses, for example the seven semesters of Chemistry, Physical and Organic Chemistry, and Biochemistry. Our students don't have enight time to take all those courses!

Even more significant is that many courses in other departments turn out to be very different from what we think of as Physics education. Our ambition in all our courses is to give students simple, general-purpose intellectual tools that tie together many kinds of apparently disparate phenomena. Many of those tools are quantitative and involve modeling of an unfamiliar situation to confirm or falsify some mechanistic hypothesis. We'd like our students to be able to face a problem they have never seen, pull the right tool out of their bag, and solve it. Do you really have a course like that in your medical school?

"That's not really physics." A course in Biological Physics can tell a story whose protagonists include Einstein, Smoluchowski, Pauling, Delbrück, Kramers, and a corresponding class of contemporary names. Are they really physicists? Such a course can also serve as an entry to the conceptual foundations of nanotechnology and soft condensed matter. It also supplies a context in which to teach ideas in continuum mechanics, practically banished from many of our curricula [4]. Is that really physics?

"Our students can't handle it." We hear this comment surprisingly often. The implication seems to be that hard courses will drive away even the few Physics majors we have left. But students work hard when they think they're getting something they need. Physical Chemistry is a lot of work, it looks good on your medical-school application, and students take it. Biological Physics can play the same kind of role.

Finally, some questions come from within:

"I'm nervous! I don't know all that stuff, and I don't have time to teach myself and create a whole new course. And what would I cover, anyway? The field is too huge!" We still feel this! It never goes away. But high-energy particle physics is huge, and somehow we teach that. In part, we're comfortable with particle physics because we took it when we were students, but more importantly it has a fairly stable canon that's clearly described in textbooks. Standard texts are now starting to emerge in Biological Physics too, together with the usual ancillary materials like problem sets (and even solutions). These curricular materials will make it unnecessary for the overburdened instructor to invent the whole course from scratch.

We have also found it surprisingly easy to get a cooperative atmosphere in an interdisciplinary class. The Biochemistry students do catch us making biochemical slips. But if we're respectful of their own uneasiness with dimensional analysis, then they end up going the extra mile to teach us things we need. Even better, a little hint is often all our students need to team up among themselves in interdisciplinary study groups.

An intermediate-level course

One way to plan a course is to fix the starting and ending points, then find a least-action trajectory connecting them. At one of our institutions, we proceeded in this way. We decided to pick up the story where our regular first-year physics courses end, and finish with meaningful discussions of single-molecule manipulation, molecular motors, and the mechanism of nerve impulses, all topics of current research interest. We then asked, what points must we visit along the way?

In a nutshell, the answer was that we should begin with simple estimates and dimensional analysis, then review a little cell biology to get the players on the stage. Next we needed a little kinetic theory, leading to the key conceptual foundation of random walks. From this vantage point we can see many of the phenomena that make the submicrometer world so different from our own — for example, the strange world of low Reynolds number [5]. We can also get a feeling for the tendency of entropy to increase, in the concrete framework of diffusion.

Only when we have a feeling for entropy do we introduce its abstract definition. But the abstract viewpoint has its virtues, as it leads us to a compact and general analysis of entropic forces. Viewing chemical forces as a particular case of entropic forces is a new experience for our Chemistry students, and one that leads naturally to the study of single-molecule devices like enzymes and molecular motors (Fig. 1). We also find it satisfying to analyze a case where an entropic force can be rigorously computed and compared to experiment, as in the mechanical extension of long molecules of DNA. Finally, we can begin to discuss the collective behavior that emerges when many similar molecular agents act in concert to create traveling nonlinear waves of excitation — the nerve impulse.

While covering this material, we have found it useful to ask students to read in parallel selections from a mainstream cell-biology textbook. There is no substitute for learning the language, and the iconography, from an industry-standard source. (Some beautiful, and technically accurate, popularizations are also quite useful, for example [6].) Also, as in any physics course, we try to get students to use computer software. Students need to get into the habit of turning to mathematical software to examine the behavior of a model; they also need the habit of turning to a molecular-visualization package, and the allied online databases, to examine a macromolecule of interest.

The syllabus just outlined will not suit everyone, of course. But it does have some claim as a conceptual framework, into which many more advanced ideas can be fitted. We think that students need the core ideas of several disciplines before they move on to more abstract topics like neural and metabolic network analysis. Whatever topics you choose to cover, we suggest that every concept be rooted in some quantitative experimental data, the same rigorous standard that we apply when framing a course in, say, quantum mechanics. As physicists, we were taught that if you can write and solve a simple little model that draws a curve through some real data, and that is rooted in concepts that explained other kinds of experiments, then you may have learned something. Of course, plenty of life scientists concur with such an ethos. We would like to instill it in students, even if it means skipping much of the voluminous factual material of cell biology.

Laboratory courses in Biological Physics

Perhaps the simplest way to incorporate experiments in biological physics and soft condensed matter into the undergraduate curriculum is by introducing them into the standard junior or senior level physics lab classes. If we ask ourselves why the current lineup of classic experiments exists (speed of light, e/m, Mössbauer spectroscopy, etc.), the answer is not that there is some particular experimental skill each teaches that is so important later in one's professional life, but rather, taken together they expose students to the interplay between theory and experiment with a healthy dose of error analysis. Viewed this way, a lab in which students examine the Brownian motion of micron-size spheres through a microscope, and thereby determine Avogadro's number as Einstein did with Perrin's observations is surely as important as one in which students measure e/m. And an inexpensive laser tweezer setup [7] to learn about optical trapping and Stokes drag must surely be as central as a Michelson interferometer to measure the refractive index of gases. This is just the tip of the iceberg.

At the graduate level the possibilities are much greater, particularly as departments embark on interdisciplinary education and research efforts such as the IGERT programs supported by the NSF. The experience of one of us with such an effort at the University of Arizona has provided the resources and students to experiment with how such a course can be structured; a detailed description is given elsewhere [8].

Combining principal investigators from Applied Mathematics, Physics, Neuroscience, Physiology, and Molecular and Cellular Biology, a centerpiece of this effort is a dedicated laboratory that is home to a course taken by all students in the IGERT program. They have come from those departments and others such as Biomedical Engineering and even Astronomy. Faced with such a diverse clientele, yet wanting to give all students a meaningful laboratory experience, we rejected the notion of a "methods" course that would simply survey current laboratory techniques in biological physics. Instead, we developed one that again puts the emphasis on the interplay of theory and experiment through a case study format. This serves the students well, for each comes with definite strengths and weaknesses. For example, graduate students in applied mathematics have no problem with the more theoretical underpinnings of the various lab experiments, but instead must learn to ask questions with an experiment, a practice which is almost totally absent from their standard curriculum. Students in biochemistry are very familiar with biological protocols, but are weak on dimensional analysis and the study of partial differential equations that describe diffusion or fluid flow. Thrown together in a lab course where cooperative learning is emphasized, these students can produce remarkable results.

A key issue is: What are the right experiments? Based in part on the research expertise of the faculty running the course, we chose to organize the experiments by length scale (Fig. 2). After introductory lecture material on the essentials of dimensional analysis and estimation, Stokes drag and the Stokes Einstein relation, electrophysiology, pattern formation, microscopy, micromanipulation, and time series analysis, each pair of students spends the remainder of the semester on one experiment. These include: (i) at the molecular scale of nanometers - investigation of the properties of individual motor proteins (kinesin) as they carry microspheres along microtubules, along with a related study of the Kramers problem of thermally-assisted hopping over a potential barrier created by two nearby optical traps; (ii) at the cellular scale of microns - measurement of action potentials in neurons of the moth *Manduca sexta*; (iii) at the scale of hundreds of microns - particle-tracking studies of bacterial chemotaxis and related fluid motions; (iv) on the centimeter scale - pattern-forming processes including bacterial bioconvection and the Belousov-Zhabotinsky reaction known for its rotating spiral waves. Each of these experiments has a very well-established underlying theoretical description. Like the experiments themselves, some of these theories are highly non-trivial. Yet, by spending much of a semester focused on both, surrounding by fellow students from a broad range of departments in the atmosphere of a research group, our students have mastered them.

The laboratory layout includes common space for the students to gather for theoretical lectures and to make oral presentations. That space also doubles as the home for an undergraduate biological physics course, in which the experimental setups serve as sophisticated demonstrations. What better way to lecture about bacterial chemotaxis than to have a suitable microscope setup three meters away so the students can see it with their own eyes?

A no-prerequisites course for biology majors and premeds

There are many ways to structure a course for students with no university-level physics course experience. For example, one could add a half-credit seminar that runs parallel to an existing version of first-year physics. A more ambitious project could be to create an entirely new version of first-year physics, geared to the needs of life science students. We will only mention one such course, taught by Jané Kondev at Brandeis University (Biological Physics 11).

The idea was that a course geared toward freshman can play an important role in getting students to think about biology in a quantitative way early in their careers. To this end, the instructor began by having the students estimate the number of buttons in the room, starting with crude arguments and then refining them. Lest the students (or readers of this article!) think this was an idle game, the next step was to get a bound on the number of ribosomes in a bacterium, given their relative sizes. Knowing the time needed for a bacterium to divide, its mass, and the molecular weight of an amino acid, the class was then able to estimate accurately the rate at which a single ribosome synthesizes proteins!

In a similar way, all the cartoons found in cell biology books suggest simple and illuminating numerical estimates (Fig. 3). In fact, stepping through such a book suggests a number of simple physical models needed to carry out such estimates, such as the random walk, beam elasticity, the ideal gas law (and its osmotic counterpart), Stokes flow, and so on. "Mathematicizing" the cartoons in this way motivates the study of these models, and also leads rapidly to discussions of current research. Students find this sort of work very empowering.

Biological Physics in an Engineering department

Although our primary topic in this article is curriculum for Physics departments, there are also opportunities to offer the material in Engineering schools. Physics undergraduates and Engineering undergraduates typically have different motivations for their respective courses of study. Many Physics students study science because of their desire to understand Nature, whereas Engineering students study science because it is the basis for technology. These differences must be respected when teaching Biological Physics to Engineers. In particular, although Engineering students appreciate the importance of fundamental understanding, and are capable of the same level of mathematical sophistication as Physics students, they are eager to know the application of a model before they are ready to give their full attention to the development of the model. Engineering students want to see the connection of their coursework to the "real world" of industry, but they are often equally keen to see how the material they learn in their traditional engineering courses (such as beam theory, plate theory, and transport theory) applies to biology. Bioengineering students are especially excited to see some of the material covered in their biology courses treated from the physical point of view.

What does all this mean for a syllabus? One approach we have found to be successful is to organize the syllabus around biological or biotechnological questions. Engineering students are particularly receptive to questions that relate to optimization or physical constraints. For example, at the beginning of the course we may introduce the phenomenology of the packing of DNA into the head of a virus. A simple question is, "How much work does it take to stuff the DNA into the head?" A natural place to start is with the random walk model of a polymer. The students are then led directly to the ideas of entropy and entropic forces. A side benefit of this approach is that it helps cement the students' understanding of entropy, which in the Engineering curriculum is typically first encountered from the abstract perspective of thermodynamics. Once the idea of an entropic force is in place, it is natural to introduce single-molecule experiments and experimental force-extension curves, and then point out the limitations of the random walk model for explaining these curves. At this point it is also useful to introduce data from experiments on DNA cyclization, which measure the probability that the two ends of the DNA polymer come close enough together to bind. The students begin to see how accounting for DNA's elastic resistance to bending and twisting explains the experiments, and are then in a position to evaluate the relative importance of elastic and entropic effects in the original question of DNA packing.

This basic approach can be readily continued for a host of topics; for example, membrane and vesicle mechanics can be motivated by a discussion of encapsulated drug delivery, or the physics of cell adhesion can be motivated by a discussion of the challenges of tissue engineering. The unity of mechanics and statistical mechanics allows us to treat these disparate topics with just a few simple ideas.

Conclusion

Creating a sustained curriculum change is a big job. But as we mentioned earlier, it's important to meet the challenge: Many Physics departments have seen significant erosion in their service teaching, and hence their internal support, over the last decade. We need to explore all possible ways to offer new courses that other departments (and their students) actually want. Moreover, we see many of our undergraduate students basing their choice of graduate school in part on the availability of Biological Physics programs. Soon we will also find high-school students choosing their college, and undergraduates choosing their major, on similar grounds.

But it's not all about gloomy numbers! It's also exciting to open new doors for students, and gratifying when they respond as they have to our courses. What's more, we have found teaching Biological Physics — a course we never took as undergraduates — to be an exciting and fun part of our own professional growth. Some of this excitement has rubbed off onto our students, then back on to us, and so on. The prospect of such stimulation is a big part of why we went into academic careers in the first place. So if you find yourself teaching this course, remember to enjoy it. And good luck.

Thanks

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References

1. National Research Council, *Bio2010: Transforming Undergraduate Education for Future Research Biologists* (National Academies Press, Washington DC 2003) (available at `http://books.nap.org`); J. J. Hopfield, "Form follows function," Physics Today, November 2002, pp. 10–11; W. Bialek and D. Botstein, "Introductory science and mathematics education for 21st century biologists," Science 303(2004) 788-790.
2. B. Alberts, "The cell as a collection of protein machines: Preparing the next generation of molecular biologists," Cell 92 (1998)291–294.
3. S. Amador Kane, "An undergraduate biophysics program: curricular examples and lessons from a liberal arts context," Am. J. Phys. 70, 581 (2002).
4. Jerry Gollub, "Continuum mechanics in physics education," Physics Today, December 2003 p10.
5. E. Purcell, "Life at low Reynolds number," Am. J. Physics 45 (1977) 3–10; H. Berg, *Random walks in biology* 2nd ed. (Princeton University Press, 1993).
6. See for example M. Hoagland and B. Dodson, *The way life works* (Random House, New York, 1995).
7. S.P. Smith, S.R. Bhalotra, A.L. Brody, B.L. Brown, E.K. Boyda, and M. Prentiss, "Inexpensive optical tweezers for undergraduate laboratories," Am. J. Physics 67, 26-35 (1999); John Bechhoefer and Scott Wilson, "Faster, cheaper, safer optical tweezers for the undergraduate laboratory," Am. J. Physics 70, 393-400 (2002).

8. R.E. Goldstein, K. Visscher, R. Reinking, L.A. Oland, and M. Tabor, "An interdisciplinary graduate laboratory for biological physics," preprint (2004).

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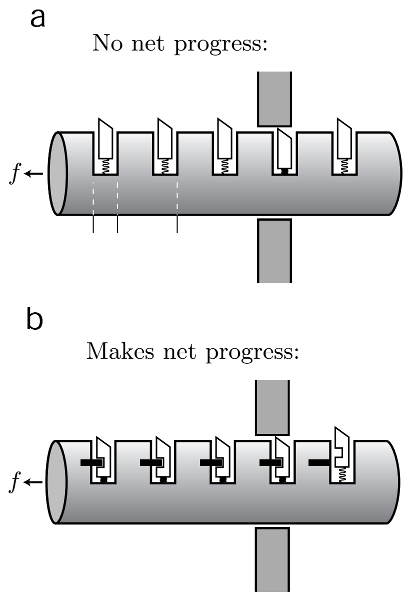


FIG. 1: Mechanical analogies can illuminate physical ideas hidden in the mass of molecular details. Naïvely, it would seem that thermal motion would drive the ratchet in (a) to the right, doing work against a load f. Once the students have worked through the microscopic details of why it *doesn't* work in this way, they are ready to study the modified ratchet in (b). This time a mechanism releases each spring-loaded pawl only after it emerges on the right side of the wall. This device may seem fanciful, but it contains the essence of an idea currently believed to underlie real molecular motors. (Adapted from P. Nelson, *Biological Physics: Energy, Information, Life* (W.H. Freeman and Co., 2004). Used by permission.)

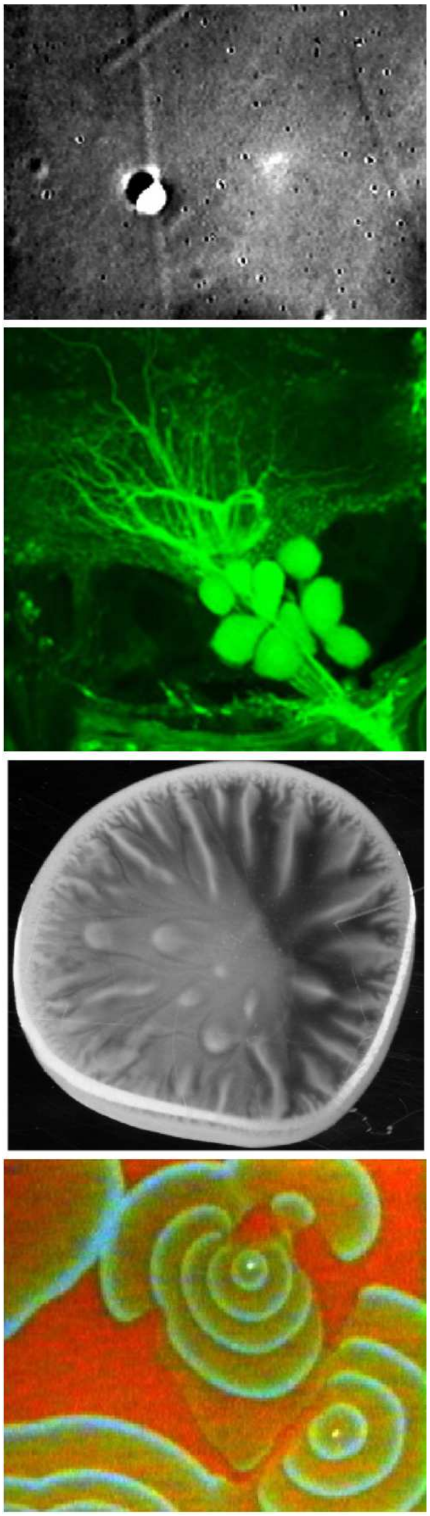
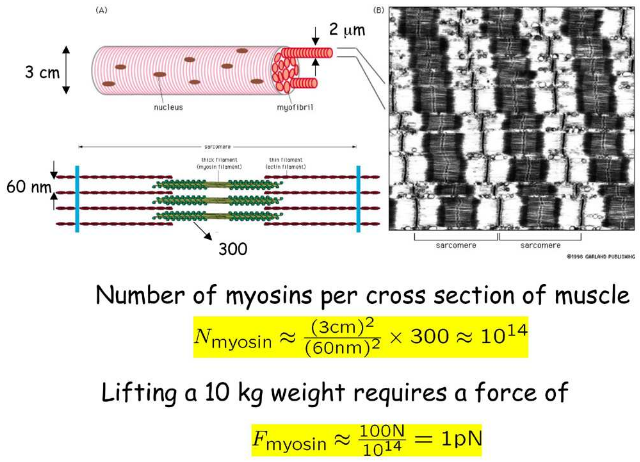


FIG. 2: Experimental themes in an interdisciplinary laboratory course for graduate students. From top to bottom: microspheres pulled along microtubules by the motor protein kinesin, fluorescently labelled ganglia in *Manduca sexta*, bioconvection patterns in a drop of bacterial suspension (*Bacillus subtilis*), spiral waves in the Belousov-Zhabotinsky system in a petri dish.



Number of myosins per cross section of muscle

$$N_{\text{myosin}} \approx \frac{(3\text{cm})^2}{(60\text{nm})^2} \times 300 \approx 10^{14}$$

Lifting a 10 kg weight requires a force of

$$F_{\text{myosin}} \approx \frac{100\text{N}}{10^{14}} = 1\text{pN}$$

FIG. 3: [[Replace with better quality]] Knowing the overall structure of muscle, and the density at which myosin filaments are packed in muscles, students can estimate accurately the forces exerted by individual molecular motors. Indeed, the stall force of a single myosin motor is roughly 5 pN. (Adapted from the forthcoming book by R. P. Phillips and J. Kondev, *Physical biology of the cell* (GET THIS CITATION RIGHT). Used by permission.)

FIG. 4: Possible cover figure. Graduate students Heather Seifert (Biomedical Engineering) and Tessa Osborne-Smith (Applied Mathematics) at work on an experiment to study action potentials. (Image courtesy of R. Reinking, University of Arizona