Teaching molecular biophysics at the graduate level

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INTRODUCTION

Molecular biophysicists use the concepts and tools of physical chemistry and molecular physics to define and analyze the structures, energetics, dynamics, and interactions of biological molecules. The recent explosion of new knowledge, methods, and needs for biophysical insight has made the development of graduate training programs much more challenging than was previously the case. 25 years ago, the question was "What to teach?" Today, the question is "How can everything that must be taught be packed into a reasonable amount of time?" At the same time, the recent influx of relatively large cadres of gifted, excited students; increasing resources, and the gradual shakedown and consolidation of the field combine to make the task more rewarding and in some ways more straightforward. Although graduate programs in Molecular Biophysics have existed since at least the mid-1960's, the recent establishment of a Molecular Biophysics Training Program by the Institute of General Medical Sciences of NIH has generated new interest. Molecular biophysicists are now much less likely to define themselves primarily as chemists or biochemists, or to disguise courses in molecular biophysics as courses in "physical chemistry for biologists."

Teaching molecular biophysics at the graduate level is difficult for the same reasons that research in the area is difficult. The potential range of the subject is as broad as physical chemistry itself, while the need to apply physical chemical concepts and techniques to large, complicated, strongly interacting molecules in solution and in partially ordered membrane phases pushes the state of the art in the physical sciences to its limits. Developments such as the theory of the helix-coil transition in double-stranded DNA, saturation-transfer EPR spectroscopy to study dynamics of membrane and muscle, and molecular dynamics simulation ofprotein dynamics, are among the most ambitious and innovative in physical chemistry in the last several decades. To achieve such advances requires deep, fundamental training in statistical mechanics, spin quantum mechanics, and similar areas. We cannot help worrying whether our students (who must spend considerable time learning about the biochemistry of proteins and nucleic acids, and about molecular genetics) are being trained to be innovators as well as informed users of sophisticated physical science. The comparison with their fellow students in molecular biology, who after a few courses dive into laboratory work that leads to ready publication, is not an easy one.

Molecular biophysics has undergone a revolution in the past several decades. When the authors of this article were students, in the 1950's and 60's, the idea that one might obtain atomic-level structures of proteins and nucleic acids was little more than a dream. A few heroic scientists struggled for decades to get crystal structures of a few proteins, succeeding at best in tracing the chain backbone and observing some ofthe basic structural features (helices and sheets) predicted by Pauling. The prediction that we would someday accumulate structures at the rate of one per week, at a level of resolution that would enable determination of arrangement of catalytic groups in an enzyme, and subtle rearrangements upon binding of ligands, seemed beyond belief. That we would be getting similar quality of information on small proteins and oligonucleotides in solution from NMR would have seemed even more unlikely. NMR had only recently been developed as a chemical tool for small organic molecules, and the enhancements that have made it feasible for macromolecules (particularly high field superconducting magnets and Fourier transform methods) were not yet conceived. The advent of supercomputers, powerful desktop workstations, and personal computers, enabling rapid analysis of huge data sets and simulation of macromolecular dynamics, was unanticipated. Lasers were not yet invented. The exquisite sensitivity of microcalorimeters was yet to be developed. The list of new technology and theory on which modern molecular biophysics depends could be extended almost indefinitely.

Our graduate curricula were crowded enough before these modern developments, with courses in thermodynamics, quantum mechanics, statistical mechanics, and mathematics, and with perhaps a course or two in (mainly metabolic) biochemistry. How can we ask our students to take the even more sophisticated physical chemistry courses they need today, along with the much greater amount of equally necessary biochemistry, genetics, and cell biology, and still have them graduate with a good thesis in five years? Frankly, we fear that we often do not do an adequate job: students in biochemistry departments don't take enough advanced physical chemistry and physics, and students in chemistry and physics departments don't take enough biology, to meet the challenges of current and future reseatch in molecular biophysics. At best, they become experts in a specialized area, and learn more by reading and self study throughout their careers (as most of us older scientists have done). But it is open to question whether today's students trained as molecular biophysicists can realistically achieve the breadth and depth of knowledge needed to progress in the future as we have in the past. Perhaps it is more realistic to look for advances to come from collaborations between deeply trained physicists and physical chemists who have some interest in molecular biology, with deeply trained biochemists and molecular biologists who have an appreciation of the potential contribution of the physical sciences.

UNDERGRADUATE PREPARATION

Because molecular biophysics is both broad and deep, laying the foundations at the undergraduate level is highly desirable. Ideally, a student entering graduate school should have a good background in physics, chemistry, mathematics, and biology. The most useful courses are the following:

Physics: mechanics, electricity and magnetism, optics, and atomic and molecular physics;

Chemistry: general, organic, and physical chemistry;

Mathematics: calculus through multivariate, differential equations, linear algebra and matrices, numerical analysis, statistics, and computer programming;

Biology: introductory biology, cell biology, biochemistry, molecular biology, genetics; and, if time permits, physiology and neurobiology.

The central discipline of molecular biophysics is physical chemistry including thermodynamics, kinetics, the various forms of spectroscopy, diffraction and scattering, and statistical mechanics. This is the discipline in which the quantitative understanding of the behavior of matter is developed in molecular terms. A typical undergraduate course, preferably a year in length, will give relatively little attention to the biological applications of these topics. However, there are some texts, such as *Physical Chemistry with Applications to the Life Sciences* by Eisenberg and Crothers (1979, Benjamin-Cummings Publishing Co. Redwood City, CA), *and Physical Chemistry Principles and Applications in Biological Sciences* by Tinoco, Sauer, and Wang (2nd ed., 1485, Prentice Hall, Englewood Cliffs, NJ), which do provide good biological examples.

In the absence of a molecular biophysics major, students can meet many of their needs by majoring in physics, chemistry, molecular biology, and biochemistry, or even mathematics. Because the path from the physical sciences to biology tends to be less arduous than the reverse, majoring in one of the physical sciences is probably best. However, students graduating with a physical science major will need to make special efforts in graduate school to develop their molecular and biological intuition, while students coming from a largely biological background especially need a solid undergraduate course in physical chemistry.

Clearly, a student must make some choices if there is to be anything in his/her life besides science, and many deficiencies can usually be made up in graduate school. A strong advising system is crucial to making intelligent, informed choices. One of the issues that the biophysical community has not dealt with very effectively is the question of setting up undergraduate majors. The historical diffuseness of the field, the paucity of interested students, and resistance from university administrators and already existing scientific communities have tended to discourage these efforts. However, times are changing, and the consolidation of the field combined with widespread interest and support argue for renewed efforts.

All the course work in the world cannot substitute for hands-on experience. Methods can be taught in formal laboratory courses, but the thrill of making a new discovery generally comes first from carrying out an independent research project. Undergraduate research is one of the best ways to convince bright undergraduates to go on to graduate study in molecular biophysics.

GRADUATE TRAINING

The typical Ph.D. program consists of roughly two years of coursework, two or three laboratory rotations in the first year, auditing and presenting research seminars, oral and possibly written prelim examinations, and roughly three years of research. In designing a graduate program, a balance must be struck between the student's short term and long term needs. In the short term, the student needs to master the methodologies that are currently state of the art in his/her field of research; in the long term, she/he will need the survival skills to move with the times. How many of the specific skills that you acquired in graduate school do you use today? At the same time, most graduate students are very goal oriented and have little patience with broad philosophical discussions, or learning that is seemingly irrelevant to the demands of the moment.

The central questions in molecular biophysics deal with macromolecular structure, energetics, and function. The most widely used methods for addressing these questions are diffraction, magnetic resonance and applied spectroscopy, hydrodynamic methods, and computer simulation. Students need three types of courses in molecular biophysics: courses in macromolecular structure and dynamics, courses in biophysical methods, and courses in physical chemistry. In order to be prepared for the future, they also need exposure to cell and molecular biology. This is a tall order, and invariably creates a tension between formal coursework and the need and desire to "get into the lab." The general rule of thumb is that students should start working in a lab during the first semester, and coursework should be largely over by the end of the third or fourth semester.

The graduate program in molecular biophysics at the University of Minnesota provides one possible model. This course is jointly taught and cross-listed between the Biochemistry and Chemistry departments; it does not have a Molecular Biophysics designator. Typically, students take several (but usually not all) of the following set of courses, in one-quarter (10 week, 40 lecture hours) modules:

Physical biochemistry: thermodynamics, binding, allosterism, intermolecular forces, polyelectrolytes, hydrodynamics, diffraction, and light scattering;

Magnetic resonance: spin physics, NMR, EPR;

Applied spectcoscopy: optical absorption, fluorescence, probes, circular dichroism, Raman and infrared;

Kinetics: steady-state, stopped flow, rapid kinetic methods, use in determining mechanism;

Protein and nucleic acid structure and dynamics: forces, mobility, crystallography, computer simulation and graphics.

It is not easy to find a suitable text for a graduate course in molecular biophysics. Currently, the leading text is undoubtedly *Biophysical Chemistry* by Cantor and Schimmel (1980, Freeman Publications, San Francisco). This comprehensive three-volume work has a range of coverage which enables many different courses to be structured by selecting certain chapters. However, it is somewhat outdated, requires a higher level of mathematical sophistication than many graduate students with biological backgrounds find comfortable, and is expensive if all three volumes must be purchased. Texts that are less demanding, but may be suitable for a short course that emphasizes mainly solution methods rather than NMR or crystallography, are *Physical Biochemistry* by Van Holde (2nd ed., 1985, Prentice-Hall) *and Physical Biochemistry: Applications to Biochemistry and Molecular Biology* by Freifelder (2nd ed., 1982, Freeman Publications). Tanford's classic text *Physical Chemistry of Macromolecules* (1961, John Wiley and Sons, New York) is probably not suitable for a modern, general course; but it has a detailed treatment of classical topics in polymer solution physical chemistry as applied to biological macromolecules which has no parallel in other texts. The recent book by Nossal and Lecar, *Molecular and Cell Biophysics* (1991, Addison-Wesley Publishing Co., Reading MA) covers an interesting selection oftopics at a good level; whether it is suitable as a text for any particular course depends on the concordance between its table of contents and the course syllabus. Most instructors will probably find themselves using one of these texts as a base, and supplementing it with additional reading.

Laboratory experience in purifying biological molecules and testing their biological activity is crucial if biophysical experiments are to be done on biologically meaningful systems. Such experience may be obtained in thesis research or rotations; but if the research lab expertise lies more in instrumentation or theory than in preparative biochemistry, a formal laboratory course may be desirable. A realistic discussion of the necessary knowledge, and where to find it, is given by Tom Pollard in the accompanying article. The use of computers in molecular biophysics is ubiquitous, ranging from data acquisition and analysis, through sequence database searches, to supercomputer simulations. Many departments have instituted courses in molecular biology computing. However, instruction in the sort of computing most useful in biophysics tends to be informal; and students often teach themselves and each other about graphics and simulation packages. FORTRAN is still an extremely useful language for scientific computation, particularly because a huge amount of already written, tested, and readily available FORTRAN code is available for all sorts of numerical analyses and simulations. However, many argue that C is the language of the future.

Although the breadth and depth of formal coursework in molecular biophysics is probably greater than in most other fields of modern biology, students also need training in how to keep up with and critically assess the current literature. Because important developments are reported not only in the standard biology journals, but also in the chemistry, physics, and computer literature, this may be an even more difficult task than in other fields of biology. Some of the journals which may need to be consulted on a regular basis in molecular biophysics per se are*: Biophysical Journal, Biophysical Chemistry, Biopolymers, European Journal of Biophysics, and Journal ofBiomolecular Structure and Dynamics*. Broader journals that publish a good deal of biophysical work include: *Biochemistry*, *Journal of the American Chemical Society, Journal of Membrane Biology, Journal of Molecular Biology, Nucleic Acids Research, Proteins: Structure, Function. and Genetics*, and *Protein Science.* Some of the most exciting advances are rushed to print in Science and Nature. The serious biophysical chemist will want to *scan Journal of Chemical Physics* and *Journal of Physical Chemistry*, while the specialist in a particular area will need to read *Acta Crystallographica, Journal of Computational Chemistry, Journal of Magnetic Resonance. or Macromolecules.* Review articles are a crucial way to gain an overview of the current status of particular fields of science. The leading review series in molecular biophysics are *Quarterly Reviews of Biophysics, Annual Reviews of Biophysics and Structural Biology, and Current Opinion in Structural Biology.*

Other issues are also important. Students need structured discussions of scientific ethics, how to choose a research problem (described beautifully by Pollard in his accompanying article on cellular biophysics), how to develop and write research proposals, and how to manage a scientific laboratory. Any intelligent student will eventually be able to solve technical problems; what students need most from their mentors is the benefit of wisdom that can come only from experience.

CONCLUSION

During the past 25 years, molecular biophysics has evolved from being little more than a smorgasbord of topics from physics, chemistry, mathematics, and biology, to a cohesive, fast-moving discipline highly relevant to both medicine and industry. Graduate programs must reflect that change and create curricula that both develop the student's scientific potential and prepare her/him for the realities of the rapidly approaching 21st century. In developing these programs, it is important to keep in mind that the development of biophysics has been slowed in the past because it has not been an attractive field for women and minorities. Establishing a tone which encourages newcomers to enter the field will in the long run benefit everyone.

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