Program Review
The Interdisciplinary Biophysics Graduate Program at the University of Michigan

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ABSTRACT:
The Michigan Biophysics Graduate Program (MBGP) was established in 1949, making it one of the first such programs in the world. The intellectual base of the program was significantly broadened in the 1980 when faculty members from a number of other units on campus were invited to join. Currently over forty faculty members from a variety of disciplines participate as mentors for the Ph.D. students enrolled in the MBGP providing our students with rich opportunities for academic learning and research. The MBGP has two main objectives: 1) to provide graduate students with both the intellectual and technical training in modern biophysics, 2) to sensitize our students to the power and unique opportunities of interdisciplinary work and thinking so as to train them to conduct research that crosses the boundaries between the biological and physical sciences. The program offers students opportunities to conduct research in a variety of areas of contemporary biophysics including structural biology, single molecule spectroscopy, spectroscopy and its applications, computational biology, membrane biophysics, neurobiophysics and enzymology. The MBGP offers a balanced curriculum that aims to provide our students with a strong academic base and, at the same time, accommodate their different academic backgrounds. Judging its past performance through the success of its former students, the MBGP has been highly successful, and there is every reason to believe that strong training in the biophysical sciences, as provided by the MBGP, will become even more valuable in the future both in the academic and the industrial settings. © 2008 Wiley Periodicals, Inc. Biopolymers 89: 256–261, 2008.
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THE NEW AGE OF MOLECULAR BIOPHYSICS

These are exciting times to enter the world of science. The rapid recent advances in molecular and cellular biology, structural biology, proteomics and bioinformatics, etc., have greatly expanded our understanding of the complex biology of living organisms and have helped identify an ever increasing number of protein–protein, protein–nucleic acid, and protein–membrane interactions that play critical roles in life processes such as signal transduction, transcription, cell division, and cellular organization and communication. It is painfully evident, though, that the structures of the majority of the biomolecules and complexes that feature in these life processes are not yet well characterized and their interactions are currently understood only at a rudimentary level. Indeed, while we often know the identity of the partners in an interaction, we do not under-

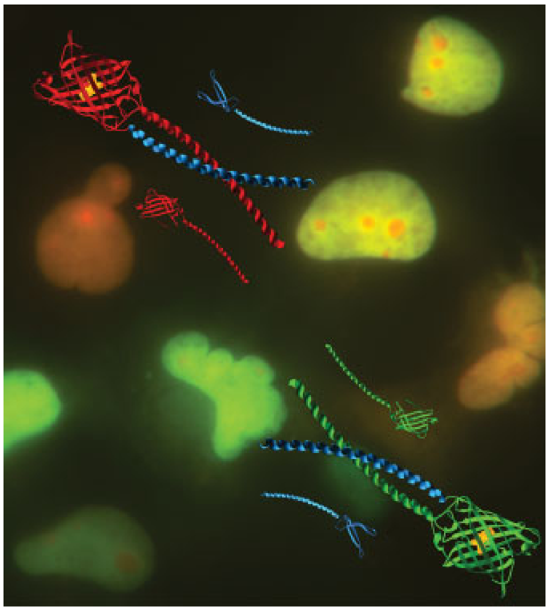

FIGURE 1 Multicolor imaging of protein interactions. Adapted from Hu and Kerppola, Nat Biotechnol, 2003, 21, 539–545.

stand how they recognize one another, what properties feature in their interaction, if and how this interaction leads to structural changes, and how all these dynamical features mediate function (Figure 1).

A deeper and more detailed understanding of these issues is obviously of immense interest and significance; however, such understanding is also very difficult to develop, as the processes involved frequently encompass multiple partners and complex interactions. The rapid advance in both conceptual and experimental approaches that took place over the last 25 years holds promise to enable us to address many of these complex systems quantitatively and in detail. Indeed, many of the techniques brought from the physical sciences such as ultracentrifugation, light spectroscopy, Mossbauer spectroscopy, X-ray and neutron diffraction, light and electron microscopy, nuclear magnetic resonance, electron spin resonance, fluorescence resonance energy transfer, and extended X-ray absorption fine structure have become everyday tools of investigation. Nobel prizes have been awarded to over 30 physicists for contributions that led directly to important advances in the biological sciences or medicine. This trend continues, and some of the newest contributions of the physical sciences are in the areas of multidimensional NMR, solid state NMR, and single molecule spectroscopy.

The introduction of quantitative physical tools into biological research has created a new discipline, biophysics, the mission of which is to apply the concepts and tools of physics and the methods of mathematical analysis to biological systems. This unique approach has provided structural and mechanistic understanding of the molecules and interactions that feature in living cells and has a critical role to play in all future advances of the biological sciences.

Biophysics, being positioned at the interface between physics and biology, is inherently an interdisciplinary science. Hence strong foundations in both physics and biology are needed to fully exploit the potential of this science. It is, therefore, crucial to develop strategies to train the next generation of scientists to meet the challenges posed by the increasing complexity of modern research. In line with this need, the primary emphasis of the Michigan Biophysics Graduate Program (MBGP) is to provide graduate students with state-of-the-art intellectual and methodological knowledge in biophysics, using a combination of course work and research experience, so as to guide and prepare these future researchers to pursue basic understanding in areas related to the molecular and cellular mechanisms that underlie all biological phenomena.

HISTORICAL PERSPECTIVE AND GOALS OF THE MBGP

The MBGP has its origins in faculty-initiated biophysical research that was flourishing at the University of Michigan throughout the 1940s and was recognized as a new discipline, in need of a formal training curriculum, in 1949 with the establishment of the Biophysics Ph.D. Program, one of the first such programs in the world. The need for coordination of the rich biophysical research activity on campus led, in 1955, to the establishment of a Biophysics Research Center that was turned into the Biophysics Research Division in 1960, and to the incorporation of the MBGP into this Division in 1963. From the very early days Michigan was at the forefront of the new discipline of biophysics, and the home of many recognized leaders including M. Beer, H.R. Crane, C. Levinthal, H.M. Randall, G. Sutherland, C. Thomas, and R. Williams.

In the late 1980s, the Biophysics Research Division broadened its research training base by inviting faculty in several other units, including biological chemistry, chemistry, microbiology, pharmacy, physics, pharmacology, and physiology, to become associated faculty in biophysics and to take part in mentoring students enrolled in the MBGP. Currently, over 40 faculty members participate in the Ph.D. program and may serve as research mentors for the Ph.D. students enrolled in the MBGP. This large faculty/student ratio is highly desirable and, as a result, no research laboratory is staffed exclusively with biophysics students, rather MBGP students typically work side-by-side with other graduate students whom their mentors draw from their academic units (physics, biological chemistry, biology, chemistry, etc.) or from other interdisciplinary programs (cellular and molecular biology, applied physics, chemical biology, macromolecular sciences and engineering). This creates a particularly multidisciplinary environment for our graduate students who learn much directly from each other and are exposed to diverse research cultures.

Several years ago, the MBGP became one of the 12 Ph.D.-granting programs to affiliate with the interdisciplinary Program in Biomedical Sciences (PIBS), the Medical School's integrated graduate program. As a result, graduate students can now enter the MBGP through two different routes, either by matriculating directly into the MBGP or by joining through PIBS. Students in the latter group spend their first year within PIBS before choosing to join one of 12 associated programs, including biophysics. This affiliation with PIBS has benefited the MBGP, and now about half of our students enter through this program.

The MBGP has two main objectives:

- To provide graduate students with both intellectual and technical training in biophysics so as to prepare them for a career in biophysical research and teaching. This is achieved by providing our students with a solid working knowledge in all the three key areas: physics, chemistry, and biology. We believe that future advances in biophysics require not just knowledge of what today's latest techniques are, but also a strong fundamental knowledge in the basic sciences relevant to this cross-disciplinary field. Such breadth is still rare even among professional biophysicists, and we believe that our efforts in bridging the gap will promote major scientific advances in the understanding of the structure and function of living organisms.
- To sensitize students to the power and unique opportunities of interdisciplinary work and thinking, and to train them to conduct research that crosses the boundaries between the biological and physical sciences. Thus, in addition to ensuring that our students acquire proficiency in the different disciplines listed earlier, the MBGP also actively promotes interdisciplinary research that is done by teams in associated laboratories. Indeed, the fraction of MBGP students who are co-mentored and who pursue their graduate work in a collaborative fashion is unusually high. We believe that this prepares our students for a future where research becomes a team effort even more than it is today.

It is very common in MBGP-affiliated laboratories that students with physics, chemistry, biochemistry, and other backgrounds come together and are trained to work as a team. The opportunity to work in this environment of a scientific melting pot encourages our students to learn each other's scientific language and acquire the missing skill sets to become biophysicists.

RESEARCH THEMES

MBGP students are offered the opportunity to conduct research in a variety of areas of contemporary biophysics including structural biology, single molecule microscopy, spectroscopy and its applications, computational biology and bioinformatics, membrane biophysics, neurobiophysics, and enzymology. These areas are concisely described below.

Structural Biology

The structural biologists use X-ray crystallography, solution and solid-state NMR, and other spectroscopies, along with computational approaches and techniques from molecular biology, to understand the function, structure, dynamics, and energetics of important biological macromolecules. Research topics range from the molecular mechanisms of bacterial pathogenesis to the development and application of state-of the-art NMR techniques to resolve the structural ensemble of noncoding RNAs and their protein complexes in solution.

Single Molecule Microscopy and Spectroscopy

In recent years, a scientific revolution has taken place in which tools to study single molecules are used to dissect biological systems and their dynamics in unprecedented detail. MBGP researchers have established a Center of Single Molecule Analysis that further pushes this envelope. Research interests within this center cover everything from proteins involved in misfolding diseases, such as Alzheimer's disease, to RNAs responsible for viral replication and the defense mechanisms of eukaryotic cells against them (Figure 2).

Spectroscopy with Biological Applications

Modern spectroscopic tools and related physical methods are used to study quantitative aspects of biological systems, from molecules to cells. Interests range broadly from following protein and RNA dynamics over the complete range of timescales of protein function—from femtoseconds to seconds—by optical and infrared spectroscopy, to monitoring the local site architecture of metal ions in biological systems—including both enzymes and cells—by X-ray spectroscopy.

Computational Biophysics

The computational biophysicists are developing theoretical approaches in protein and nucleic acid folding, computational drug design, bioinformatics, and systems biology. Large computer clusters are used to support students in very complex calculations of molecular structure, dynamics, and chemical reactivity.

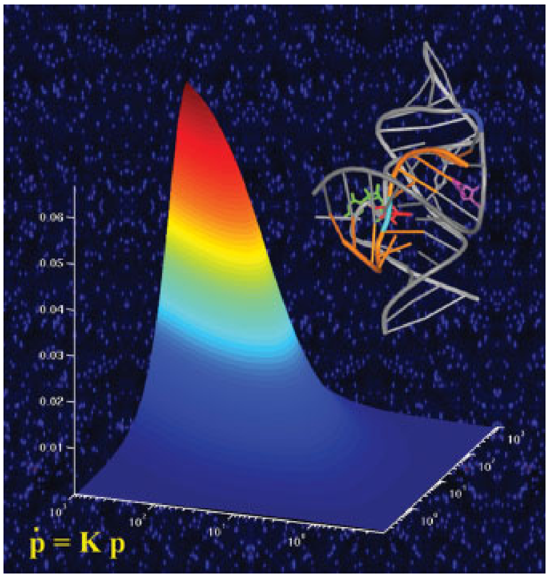

FIGURE 2 Catalysis by the hairpin ribozyme (stick figure) is monitored in real time by single-molecule FRET Microscopy (background). The enzyme is accelerated by tertiary structure formation (3-D plots). Adapted from Rueda et al., Proc Natl Acad Sci USA, 2004, 101, 10066–10071.

Membrane Biophysics

It is estimated that one-third of all eukaryotic proteins are membrane bound. Membrane proteins fulfill a variety of critical functions, with many acting as enzymes, regulating transport processes, and playing a central role in intercellular communication. At Michigan, structure determinations of membrane proteins, which are difficult to crystallize, are made possible by recent advances in solid-state NMR spectroscopy. Other research focuses on topics ranging from posttranslational modifications of membrane-bound central nervous system proteins to the population response of neurons to outside stimuli in live animals (Figure 3).

Enzymology

Researchers in this area are actively working on all aspects of enzyme structure and mechanism. Biophysics faculty integrates many of the techniques described earlier in the study of a wide variety of enzyme reactions, often in the context of understanding diseases or for environmental applications.

Neurobiophysics

Applying basic physical principles, researchers are gaining insight into the operation of the nervous system by investigating the structural complexity and spatiotemporal patterning of neuronal networks. Two basic paths are being pursued, their aims being: understanding the relation between network dynamics and its underlying topographical structure, and identifying temporal links formed during evolution of the network. Understanding both temporal and spatial interdependencies formed within the network is crucial for identification to dynamical correlates of brain function (e.g. memory formation and reactivation) during cognitive processing as well as in pathological states such as epilepsy (Figure 4).

OUR STUDENTS

There are two constituencies served by the Biophysics Graduate Program: students with training in the physical sciences (physics, chemistry, engineering, and mathematics), who wish to apply their expertise and perspectives to biological systems, and students with background in the life sciences (biology, biochemistry, molecular biology), who wish to incorporate the powerful tools of the physical sciences in their work. Historically most of the students entering the program have come from the physical sciences. This is changing as the association of the MBGP with the Medical School's PIBS has increased our exposure to students with undergraduate degrees in the life sciences. The broad distribution of research interests, and expertise, among the MBGP faculty and the fact that many of them focus their research on important biological problems is also attractive to this cohort of students.

While prior education in the physical or biological sciences are both excellent routes for students to enter the MBGP, one can envision a more direct way, a degree conferring undergraduate program in biophysics. Very few such pro-

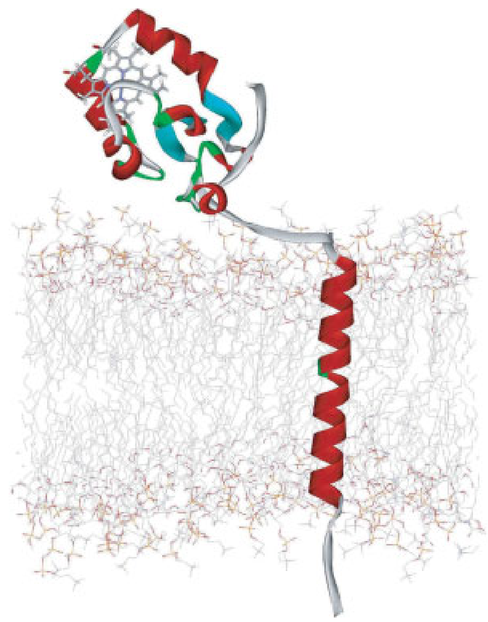

FIGURE 3 Molecular model of membrane-bound cyt-b5 from solid-state NMR spectroscopy. Adapted from Durr et al., J Am Chem Soc 2007, 129, 6670–6671.

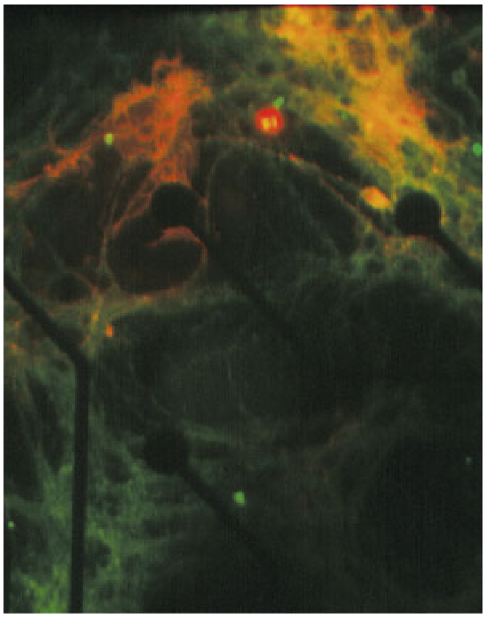

FIGURE 4 Analysis of neural activity recording of hippocampal cell culture (using multielectrode arrays primary) is augmented by immunofluorescence studies of network structure. Courtesy of Dr. M. Zochowski, University of Michigan.

grams exist worldwide. As a testimony to the University of Michigan's recognition of the importance of training in biophysics, the university has recently established an undergraduate degree in biophysics and has charged the MBGP faculty with developing the curriculum and administering this new program. This will create a new body of potential graduate students for the MBGP and is a clear indication of the continued commitment of the University to a flourishing biophysics community on campus.

In addition to our strong commitment to provide outstanding educational opportunities to our students, the MBGP is also committed to the recruitment and training of a diverse body of students. Thus, the inclusion of women and of students from diverse ethnic and cultural backgrounds in our program is viewed as a critical component of our mission. On a larger scale, the University of Michigan is committed to, and actively pursuing, the recruitment of a diverse pool of both faculty and students so as to maintain, and strengthen, the diversity in the University campus.

COURSEWORK AND THESIS RESEARCH

With the diversity of incoming students it is important to ensure that we provide high-quality education in the multiple areas of biophysics without overwhelming the students and, at the same time, that we make graduate school a time-efficient experience (at present, the average time to graduation for biophysics students is 5.6 years).

The MBGP addresses this challenge by offering a curriculum that aims to accomplish two goals: (a) to provide a common academic base and (b) to accommodate the different backgrounds of the students. Consistent with our interest in broadening our student body, we have worked to increase the program's flexibility while enhancing the student's exposure to the core concepts in biophysics.

We now require coursework in three areas, the physical sciences, the biological sciences, and biophysics. The physical science requirements are designed to give students at least an advanced undergraduate understanding of quantum mechanics and thermodynamics. The biological sciences requirements ensure that the students are conversant in biochemistry, cell biology, and protein structure and function. All MBGP students take the two core courses in biophysics: biophysical chemistry and biophysical techniques. Three additional electives are required of each student. Often these are chosen from other courses offered by the unit, including dynamical processes in biophysics, X-ray crystallography of macromolecules, biophysical principles of microscopy, and multidimensional NMR spectroscopy. After including undergraduate coursework, a typical student required to take seven or eight courses, typically finishing their coursework sometime in their second year.

To custom-fit the curriculum to the specific needs of individual students, faculty advisors consult with students to design for each a list of courses that meet the guidelines and, at the same time, satisfy the specific goals of each individual. For example, cognate courses and electives are chosen to assure that each student attains competence in the broad areas of physics/physical chemistry, biophysics, biochemistry, and cell and molecular biology. For students with a background in chemistry or physics, typically at least two cognates are chosen from the biochemistry/cell and molecular biology group and one from the molecular biophysics group. For students with degrees in the biological sciences, two cognates are selected from physics/chemistry and at least one from molecular biophysics or cell and molecular biology.

To familiarize incoming students with the different research topics, and laboratory environments, offered by the MBGP, all first-year students take part in term-long research rotations among the various biophysics faculties. Students typically perform two or three research rotations in their chosen laboratories before selecting a research advisor. This rotation system accomplishes three goals:

- It helps students make more informed decisions about research focus and thesis advisors.
- It gives students a broader overview of different areas of biophysics and helps them establish contacts with various members of the program.

- It provides the students with a physical and psychological "home" during the initial orientation year.

PAST PERFORMANCE AND FUTURE PROSPECTS

It is always instructive to evaluate how well a program is doing and to identify areas for improvement. One way to do so is by looking at the fortunes of past biophysics students to obtain an idea of how well our graduates succeed after they step into the "real world." By the end of 2007, the MBGP will have graduated some 30 students during the previous 15 years. As in all other biomedical fields, biophysics graduates are expected to be postdoctoral fellows in one or two laboratories before being considered for academic positions. Postdoctoral positions are also rapidly becoming a part of the training required for many industrial positions. Indeed, most our graduates went through this additional training, typically in first-rate laboratories at Stanford, Caltech, Harvard, the University of Illinois, the Weizmann Institute, Northwestern, and UC Davis. Some sought experience in industrial laboratories such as at Pfizer Pharmaceutical Company.

Following postdoctoral training, our students have been very successful in securing faculty positions at outstanding institutions such as Yale, Cornell, MIT, the University of Michigan, the University of North Carolina, Swathmore College, Brandeis, etc. Some opted for industrial positions in companies ranging from large pharmaceutical companies (Pfizer and Glaxco Wellcome) to biotechnology start-ups (Protein Pathways). There are a few students who are pursuing employment in nontraditional areas. For example, one former student is a scientific advisor for the Ratner & Prestia Law Firm.

Looking ahead, the future looks very bright for students with training in biophysics both in the academic world and in the industrial setting. The exciting recent developments in molecular and cellular biology as well as the success of the human genome project have directed attention toward the application of quantitative biophysical tools (for example, bioinformatics, computational biology, structural biology, and single molecule microscopy) that can help mine the large amount of data and convert it into new basic understanding. Pharmaceutical and biotechnology companies are also placing an increased emphasis on basic scientific research, and there is a rapid increase in the number of new biotechnology companies. On the academic front, many universities are interested in recruiting faculty with the type of rigorous interdisciplinary background that students receive in the MBGP.