Challenges at the Interface: BioMaPS*
Integrative Research among the Biological, Mathematical and Physical Sciences*, **

In recent years, divisions within the Directorate for Mathematical and Physical Sciences have seen increasing numbers of proposals that focus on biological applications at all levels of biological organization, ranging from the sub-cellular level to the environment. At the same time, divisions in the Directorate for Biological Sciences are receiving significantly more proposals that incorporate approaches from and address questions that have traditionally been the domain of the mathematical and physical sciences. Despite efforts at the divisional levels to address the increasing need demonstrated by their research communities, disciplinary panels continue to struggle with review of proposals that tackle challenges at the interface, often downgrading them as not having sufficient intellectual merit in the context of the core discipline, even when this type of synergistic research will open up new avenues of exploration in their field. It is time to address the challenges involved in identifying, evaluating, and funding innovative research at the interface of the biological, mathematical, and physical sciences. New mechanisms of identifying emerging opportunities, joint or interdisciplinary review and long-term and significant funding are needed.

Starting with basic principles, many questions within the biological sciences have been framed in terms of the underlying mathematical and physical properties over the centuries. During the 1920's, Alfred Lotka, known for his role in developing the Lotka-Volterra model of predator-prey dynamics, proposed that the Darwinian concept of natural selection could be quantified as physical law. In his 1944 book, *What is Life?,* Erwin Schrödinger asked, "How can the events in space and time which take place within the spatial boundary of a living organism be accounted for by physics and chemistry?" Today, the mathematical and physical sciences do not serve simply as tools for studies in the biological sciences, but are poised to play a much more critical role in advancing biological research. Additionally, the study of biological questions necessitates new developments in the mathematical and physical sciences, leading to new theory and experimental techniques. Indeed, as noted in the National Academy study, *BIO2010,* "Biological concepts, models, and theories are becoming more quantitative, and the connections between the life and physical sciences are becoming deeper and stronger." Even more recently, another report entitled *Research at the Intersection of the Physical and Life Sciences* reiterates this even more strongly, "It is becoming increasingly irrelevant whether a particular research topic fits neatly into one discipline or another; in fact, many of the most interesting scientific questions and pressing societal issues will require the collective expertise from multiple fields." In order to tackle the most challenging problems in biology, it is critical to have true integrative and collaborative research at the interface of the biological, mathematical, and physical sciences.

Importance and Cross-Cutting Nature. Innovative and transformative research frequently occurs at the interface of the disciplines, yet often this is difficult to recognize at an early stage. Illustrations, including the following examples, exist that demonstrate the need for collaborative research. These examples represent scientific questions at the forefront of this interface and range from scales of ecology and environment down to genetic levels, often encompassing more than one level of organization.

Although there many grand challenges in the life sciences that can and will be addressed by the collaboration of Mathematical and Physical Scientists with Life Scientists, we now describe some examples of interdisciplinary research topics:

Underlying Physical Mechanisms and Theories of Biological Systems—From Microarrays to Living Cells; From Cells to Living Systems: Biologists currently consider phenomena at various levels of organization, from gene to population to ecosystem, which emerge from complex interactions among simpler entities. These phenomena depend fundamentally on the potential for rapid adaptive responses to dynamic biotic and abiotic environments. Theories underlying these interactions need to extend beyond a particular talon or level of biological organization to account for general phenomena occurring independently at multiple levels of organization. New concepts are needed and mathematical and computational modeling, e.g., the adaptation of network theory, can surely play an important role in their discovery, as well as facilitate the reconstruction of the integrated activity of a living cell using physical and chemical information that has been gleaned from studies of cellular components conducted to date largely *ex vivo*. Additionally, understanding how cellular organization and function emerge from the underlying physical properties of the building blocks of living cells not only requires new quantitative theories, but also necessitates innovative dynamic *in vivo* experiments and the development of associated techniques. The creation of new theoretical frameworks and overarching concepts are required to encompass the richness of biological complexity. This requires the joint efforts of biologists, physicists, mathematicians, chemists, and materials scientists. Simple applications of existing theories, whether from physics, chemistry or biology, fall short of being able to capture the fundamental concepts required for groundbreaking advances.

Biological Interactions From Environment to Cell—The Physics, Chemistry and Mathematics of Boater: Biological systems are constrained not just by biological factors but also by factors that are properly the realm of physics, chemistry, and mathematics. Examples abound, from the realization that quantum effects are likely at the root of magnetic orientation in birds and turtles to the ability to synthesize unnatural amino acids that can be used to prevent enzymatic degradation of peptides. Among the areas where the biological, mathematical, and physical sciences overlap are: The movement of organisms through fluids, the mechanical behavior of hierarchical materials, the surface properties of biomaterials including both adhesion and friction, the mechanisms of cellular movement, and the design and development of nana-structured biomaterials, ranging from the reconstruction of the 3-D structure of DNA and proteins from genetic sequences to artificial organs. While such research often begins from a biological point-of-view, progress in understanding depends critically on application of physical, chemical, or mathematical principles. This occurs at various scales, from the locomotion of lizards through granular solids to the development of synthetic materials that can predictably interface with living cells. Clearly, these are problems that will only be answered through collaborations between the biological, mathematical, and physical sciences.

Physical and Chemical Constraints to Adaptation: Understanding the genotype-phenotype relationship remains a key challenge across biology, and is necessary to predict how organisms will respond to climate change. This is an area in which a closer fusion of chemistry, physics and mathematics with molecular and cell biology, organismal biology, and evolutionary biology, could catalyze major advances in tackling both basic and applied questions relating to climate and anthropogenically-induced environmental change. For example, the ability to make site-specific modifications of macromolecules through chemical synthesis now allows researchers to manipulate genetic sequences and experimentally test how modifications in DNA affect the cell. Furthermore, the synthesis of small molecules to manipulate gene activation and silencing is giving rise to the field of chemical epigenetics. Epigenesis, or the chemical modifications of DNA that lead to changes in gene expression, likely contributes significantly to genetic evolution, and the search is on for evidence that this is strong or common in nature. This search is hampered because the interactions at the genetic level are not well understood, and they no doubt involve non-linear and multivariate interactions and expression pathways. Solutions to the riddle of epigenesis, to a thorough understanding of the genotype-phenotype relationship, and to the long-term consequences of climate change lie at the research frontiers of mathematics, chemistry, and biology.

Urgency for action. The increasing availability of quantitative biological data at all levels of biological organization (e.g. genetic sequences, DNA and protein structures, ecological census and biometric data, etc.) is driving scientists from many fields towards biological systems, and this is leading to a more quantitative approach to many areas of biology. The importance of interdisciplinary research is repeatedly acknowledged, but in many ways it is still in its infancy and is not always well regarded, especially by organizations that are focused on fostering their specific disciplines. For example, most of the MPS divisions support research that seeks to understand cellular mechanisms, but fundable proposals tend to primarily serve the interests of the disciplines. Quotes from program announcements define successful proposals as "studies … that focus on the chemistry and the design and synthesis", "projects in which lessons learned from the biological application also expand the intellectual range of physics", or "projects that are mathematically innovative". While NSF supports bits and pieces of research on interdisciplinary topics in many of its programs, there is no coherent effort currently to address these important questions at the border of the physical, mathematical, and the life sciences. The approaches that underlie quantitative theories of the life sciences are the natural domain of the mathematical and physical sciences. It is critical to find ways to encourage researchers to collaborate in order to provide opportunities for them to learn each other's language, to understand the key questions and challenges in each other's field, and to transform the way research is done at the interface.

Clearly, developing appropriate mechanisms to do this will be a challenge. We believe that collaboration between the disciplines is the key and this will be a requirement on all proposals considered by this joint program. However, a significant problem we face is how to solicit, identify, and review proposals that address research at the interface. As a simple illustration, we have examples of proposals that required review by three panels in order to receive appropriate co-review. Clearly this is a strain on the reviewing community and too often such proposals are downgraded by the disciplinary panels despite having significant scientific merit. We must be ready to adapt as we seek to fund the most innovative research that advances synergistic developments that will ultimately open new avenues of exploration in the disciplinary fields.

Examples of successful programs do exist as templates. For example, the theory of and discovery of how the brain works, e.g., is a grand challenge level topic now being explored in a joint program between many institutes at the NIH and multiple directorates at NSF (specifically, the Collaborative Research in Computational Neuroscience Program (CRCNS)). Another long-standing joint program exists between NIH and NSF, a jointly funded program by NIGMS and the NSF Division of Mathematical Sciences. However, both programs have relatively narrow foci and we deem that it is a critical time to explore opportunities to do this in a way that plays to two of the primary strengths of NSF: The Foundation's focus on basic and fundamental research and the abilities of BIO and MPS to work closely together in a collaborative way.

MPS-Life Sciences Proposal: We propose a program that specifically solicits proposals that require two or more investigators, at least one with a background in the biological sciences and another in the mathematical or physical sciences. Given the range of research at the interface, different areas such as those illustrated above would be highlighted each year as the program seeks to foster novel interdisciplinary fields, with changes made to include emerging fields as the program progresses. Proposals would be reviewed by newly constituted interdisciplinary panels and final decisions would be made by a committee of program officers representing the various disciplines as well as the Office of Multidisciplinary Activities within MPS and Emerging Frontiers within BIO.

Additional Issues

Training Challenges at the Interface. We recognize that truly collaborative work requires researchers to understand the language of each other's discipline. Transitioning from disciplinary research to interdisciplinary collaborations typically requires a significant time commitment for faculty and interdisciplinary training at the student and postdoc levels requires support and commitment from all disciplines involved. As noted in *BIO2010,* "Beginning exposure to [scientific topics beyond the range of traditional biology] early is one key to educating [biological] researchers who deal easily with interdisciplinary research projects." Also, "For truly interdisciplinary education to be achieved, administrative and financial barriers to cross-departmental collaboration between faculty must be eliminated."

A few programs have attempted to address some of these issues. These include *Interdisciplinary Training for Undergraduates in the Biological and Mathematical Sciences* (UBM), *Integrative Graduate Education and Research Traineeship Program* (IGERT), as well as *Interdisciplinary Grants in the Mathematical Sciences* at the faculty level. However, more efforts are clearly needed, with efforts to involve more of the disciplines within the biological, mathematical and physical sciences.

We also plan to host both intra- and inter-agency workshops to define and promote emerging topics of relevance to this BIO/MPS interdisciplinary program as well as to determine what are its educational/training needs and the best means of creating research communities/networks at this important intersection of disciplines. It will also be very important to use these workshops to not only define emerging opportunities, but to also develop methods to determine what are we not doing, i.e., what research areas or fundamental discoveries have gone unnoticed or have been neglected because of the lack of such a concerted effort of intellectual capability and creativity.

Schrödinger, E. *What is Life?: with "Mind and Matter" and "Autobiographical Sketches",* Cambridge University Press, 1992.

BIO2010: Transforming Undergraduate Education for Future Research Biologists, The National Academies Press, 2003.

Research at the Intersection of the Physical and Life Sciences, The National Academies Press, 2010.

*Please note that this report focuses on some of the new opportunities for and funding needs of research and education programs that occur at the intersection of the Life Sciences and the Mathematical and Physical Sciences. Of course, there are equally important programs that can and should be explored at the intersection of Engineering, Math and Physical, and the Life Sciences. Since first creating this document in February, 2010, NSF's MPS, BIO and Engineering Directorates have now joined forces to create a truly integrative interdisciplinary program called BioMaPS. As stated by NSF Director Suresh in a recent presentation regarding the FY12 budget, "....BioMaPS, or Research at the Interface of the Biological, Mathematical and Physical Sciences and Engineering, seeks to integrate research from those disparate fields to lead to new theoretical and experimental techniques.

The novelty of the BioMAPS approach is the strategic investigation of living systems across scales from atoms and molecules to organisms to environment, and the application of that knowledge to develop new fundamental understanding and new technologies.

While the topics are not new, recent advances in genomics, synthetic biology, nanotechnology, analytical instrumentation, and computational and data-intensive science and engineering enable us to make significant progress in ways that were not possible even a few years ago".

**Please also accept the fact that this is very much a working or "living" document and we expect to modify it regularly as new ideas and priorities emerge.