

Bridging the Sciences: What Scientific Opportunities Are We Missing?
Prepared by the Bridging the Sciences Coalition
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AN OVERVIEW: WHAT OPPORTUNITIES ARE WE MISSING AND WHY?

What opportunities are we missing in US basic research due to inadequate mechanisms to support discovery at the interface between the life sciences and the physical, chemical, mathematical, computational and engineering sciences?

The United States does not provide sufficient support for research where the *applications* are seen as being too close to disease, biomedicine, or drug discovery for DOE or NSF funding, and where the *foundations, methods, principles, and problems* are too physical or quantitative for NIH funding. For example, if you wanted to apply X-ray crystallography, nuclear magnetic resonance (NMR), or mass spectrometry to determining the molecular structure of a protein, NIH could support it. But if you wanted to invent the next technological advance beyond those methods, especially if the technology development involved the development of some new basic science, and did not yet have a proof of principle on an important biological problem, NIH would not typically support it. NSF and DOE do support basic physical science, but with the exception of physical research having direct application to disease or biomedicine. Our federal research funding occurs largely within traditional silos and misses key scientific opportunities for progress in the 21st century.

The interface between the physical/mathematical/engineering and life sciences is neither small nor unimportant. Nobel Prizes have been given for work at the physical/mathematical and life sciences interface. Notably, many of the most important developments have come from outside the United States. For example, the development of X-ray crystallography to determine protein structures was done by Perutz at the MRC in Cambridge England; fiber diffraction for DNA was done by Rosalind Franklin and interpreted by Watson and Crick in England; NMR for proteins was done by Ernst and Wuthrich in Switzerland; the electron microscope was invented by Ruska in Germany; electron microscopy for large biological complexes was done by Derosier and Klug, and Henderson and Unwin in England; scanning tunneling microscopy for a range of problems in chemistry and biology was done by Binnig and Rohrer in Switzerland; and the patch-clamp method for membrane proteins was invented by Neher and Sakman in Germany. Each of these technologies has led to Nobel Prizes and has transformed biological science research in the United States (and everywhere else). Many of the successes of American biomedical science have been built on a foundation of methods developed elsewhere. This is not a sustainable model for leadership. Both our world leadership and our national health will suffer if we continue to miss research opportunities because of our funding silos. To sustain scientific and economic competitiveness, the United States must address scientific challenges for which one field of research pays off for another.

Biomedical research continues to march towards the ever more quantitative and the ever more microscopic, with the added imperative to connect the microscopic realities with a quantitative understanding of cells, tissues, organs, and organisms as systems. Modern drugs are invented one atom at a time, but must be tested for the effects they have on complex massively interconnected biological systems. The limits of our knowledge in the biological sciences are increasingly the result of limitations of our knowledge at the interface with basic chemistry, physics, mathematics, and computer science. These limitations are striking in light of their huge importance for our society. The health and drug industries are increasingly searching for new ways to innovate.

WHY THE BRIDGING THE SCIENCES DEMONSTRATION PROGRAM?

To accelerate our progress both in biology and in the physical sciences, we need quantitative science-driven research at this interface. The NIH Reform Act of 2006 created a Bridging the Sciences Demonstration Program that is directed toward satisfying this need. Its funding through the Director's office reflects a recognition that such cross-cutting upstream basic science could benefit research at all the NIH Institutes and Centers. In order to encourage the kinds of deep innovation that emerge from one field to pay off in another, the ideal Bridging program would involve short grant proposals, reduced reliance on preliminary data, increased reliance on the promise of the PI, with more focus on the importance of a scientific question or technical challenge and less focus on immediate biological payoff. Such proposals would be reviewed by panels of visionary scientists from appropriate disciplines, even from outside the traditional NIH purview. The mechanism should allow for proposals that range in size from small to large, and in duration, perhaps some even longer than the traditional five years, in recognition that deep innovation can sometimes take a long time both for its implementation and also for its translation to medical practice.

EXAMPLES OF GAPS IN KNOWLEDGE AFFECTING BIOMEDICAL RESEARCH PROGRESS

(1) Deep physics/computer/math problems that underpin disease or drug discovery.

Computational biology is the field that aims to replace expensive lab bench experiments for discovering new drugs with faster and cheaper computer modeling. Much of computational biology depends on physics-based, atomically detailed forcefields, such as CHARMM, AMBER, or OPLS. Computational biologists need better potential functions – a better quantum mechanical understanding of interatomic interactions, better statistical mechanical models of aqueous solvation and biomolecular association, forcefields that accurately treat atomic polarizabilities, and good global optimization methods for finding the stable molecular structures of proteins. We don't have good models of protonation states and proton transfer in biomolecules; these are important for biological mechanisms of action. NIH supports applications of existing physical approaches to biological problems. However, what has been vastly, even famously, unsupported is work to improve the physics/math underpinnings in those models, in order to improve their quantitative accuracy.

We must also develop multiscale methods, to bridge time and distance scales from the attosecond scale of electronic and atomic vibrations to the much longer and larger scales on which macromolecular and cellular processes take place. This requires essentially the development of a new statistical mechanics to describe the behavior of macromolecules in the soft condensed matter that comprises living systems. It is not foreseeable, for example, that we will be able to directly predict by atomistically detailed computation the formation of domains and the nature of phase transitions in biological membranes, let alone the self-assembly of macromolecular complexes. Statistical mechanics for the "living state"---heterogeneous soft condensed matter containing complex molecules self organized by a combination of electrostatics and van der Waals forces---is a frontier for fundamental deep science. Its development is essential to understanding the physical foundations of systems behavior in biology.

(2) Methodologies from the physical/math sciences. Biomedical research relies heavily on methods that were developed within the quantitative sciences: x-ray crystallography, mass spectrometry, nuclear magnetic resonance, MRI, optical spectroscopies, single-molecule methods

based on optical traps, chemical separation methods including high-performance chromatographies, mathematical transforms, CAT scans, PET scans, sonograms, electron microscopes, atomic force microscopes, methods for DNA and protein sequencing, solid-phase synthesis methods, RNA and protein microarrays, BLAST and other sequence-search methods for genomics, and synchrotron radiation for determining the structures of biomolecules. When such methods have reached a late stage of development, where they can be applied to biological problems, NIH will support those applications. In contrast, obtaining support for the early-stage development of such technologies is very difficult until there is a “proof of principle” for an important biological application. Hence, the “catch 22”: we lack a vehicle to develop such new technologies in the first place. Such developments are too foundational for support from the pharmaceutical or biotech industries and fall outside the current scope of the NIBIB at NIH, which focuses primarily on bioengineering and imaging.

(3) Theoretical modeling that is not experiment-driven. NIH supports computational models in biology, but almost exclusively only if such models can explain existing experimental biological data. Yet, the history of physics shows another important road to insight: the development of principles, theories and models for which no experiments yet exist. Arguably, theoretical modeling became most prominent in physics in the 1920’s, with quantum mechanics and relativity, when these new theories led to predictions so unexpected and so non-intuitive that they preceded the important experiments – rather than following them. To develop proper theory -- particularly bold, innovative theory that can lead science in genuinely unexpected new directions -- requires testing principles, approximations and assumptions against other models or simulations, in the absence of experiments. One classic example is Einstein’s “thought experiments”, which served to explore the limits of known principles, predating experiments, in the case of Mercury’s perihelion, by nearly a century. More pertinent here is the example of a 1956 3-page *Nature* paper by Crick and Watson on viral assembly, three years after their famous paper on DNA structure. At that time it was not clear whether a viral capsid was one super-protein or many small proteins; nor were the symmetries of viral capsids known. Crick and Watson gave fundamental geometrical and physical arguments predicting that capsids would be multi-protein, and be cylindrical or icosahedral. Their theory drove the development of higher-resolution electron microscopies and X-ray diffraction experiments, and is now the basis for modern structural virology. For physicists, mathematicians, and computer scientists working on such problems today – even outstanding ones - the barrier to NIH support is prohibitive.

Theoretical modeling that is not experiment-driven is largely foreign within the NIH-supported community. However, the lack of such a community is a bottleneck to progress in complex systems biology, where “emergent” properties of biological circuits are not evident from the smaller component parts, and where we currently have no body of experimental principles to guide us. Think about the big questions: what properties define alive vs. dead or diseased vs. healthy? How will we answer these questions? The answers will require a bold new way of thinking about cells as physical and mathematical networks of circuits, which in turn will require a new funding mechanism. On the horizon are cells created by synthetic biology, perhaps as new therapeutics. We need conceptual models that can help us design them.

(4) Big physics equipment for biomedical research. Support has frequently been slow to materialize for methods that are regarded as being at the physical science boundary of NIH’s mission. The utilization of the San Diego Supercomputer by biologists grew from 5 percent to 20 percent in only the past ten years. In addition, twenty five years ago, synchrotrons were mainly used by physicists. A revolution in biology took place, beginning about fifteen years ago, as biologists

found that they could get much better structures of proteins at synchrotron beam lines, and began to overwhelm those facilities. Now, roughly 40% of Stanford's SPEAR ring is utilized for biology experiments. Yet NIH funding expanded so slowly that some crystallographers, like UC Berkeley's Tom Alber, gave up and sought funding for biological beam lines through private investors instead of through federal funding. An important development on the horizon is the X-ray free electron laser, which, when successful, will give us 3D holograms at the atomic size scale; this will be a huge advance for understanding protein structures and dynamics, and the visualization of biological mechanisms.

Such limited support has also affected the biological fiber diffraction community, who also work at synchrotron beam lines. Fiber diffraction, which is a technique in which the scattering of X-rays gives the structures of partially disordered fibrous materials, has contributed to biology since the first crude structures of proteins in the 1920's. Recently, this method has renewed importance because of the many diseases – Alzheimer's, Mad Cow, Parkinson's and others – in which the structures of amorphous fibrous aggregates contribute to the disease process. Yet, resources for fiber diffraction are small. In contrast to crystallography, fiber diffraction requires a custom-tailored apparatus for each project. This is because, while *protein crystals* are laboratory "artifacts" that can be standardized and mass-produced to facilitate experimentation, each type of *protein fiber* is itself a unique type of biological assembly. So, fiber diffraction experiments are highly individual, reflecting the particulars of the biological assemblies they explore. Synchrotron beamlines for fiber diffraction were slow to appear, particularly in the US. Now, we have the BioCAT beamline at APS, Argonne, and the Biological Small-Angle X-Ray Scattering Beamline 4-2 at SSRL. However, BioCAT is not sufficiently supported by NIH, and 4-2 is funded primarily for small-angle scattering. In addition, fiber diffractionists need large magnets (the size of a large NMR magnet, but without the high-field homogeneities), specimen preparation facilities close to the beamlines, and beamline equipment – specimen holders, temperature and humidity controls, beam tunnels – built for the beamlines, but flexible enough to accommodate a wide variety of specimens. The US is considerably behind the UK, France, and Japan in the provision of such facilities. For timely payoffs to biology from the physical sciences, we need new policies that break down the funding silos.

(5) Advances in synthetic chemistry and chemical biology. As more complex molecules become drug candidates and reagents for biomedical research, we need new methods for efficient chemical synthesis of these molecules, new catalysts for these reactions, and a major focus on the development of efficient, selective chemical syntheses in aqueous solution. We also need sensitive methods for detecting and quantifying the products of chemical reactions involving drugs, cellular metabolites, and environmental toxins in cells, tissues, and organs.

MISSED OPPORTUNITIES IN RESEARCH

In order to be concrete, here are a few hypothetical proposals and vignettes, illustrating the missed opportunities that could have an enormous impact on biomedical research. This list is not meant to be exhaustive.

(A) Some Example Proposals:

(1) Quantum mechanical treatments of hydrogen bonding, to improve drug discovery. Computer algorithms to determine protonation states and proton transfer events in proteins, for enzyme mechanisms. Computer-based global optimization methods, to compute protein folds and drug

binding to proteins. Models of crystalline forms of drugs, to solve drug solubility problems. Statistical mechanics of fibrils, of water, of protein solubilities, to understand folding diseases and solve problems of biotechnology. Models of off-target ligand binding to proteins, for improving ADMET properties of drugs. Quantum mechanical ways to determine accurate electrostatic charges for computer simulations of drug molecules. As is true in many other cases, important applications to biomolecules will not happen until the foundations are built and tested on simpler chemical model problems.

(2) New magnet technologies, to get higher-field NMR and MRI technologies and higher-resolution biomolecule structures and dynamics. X-ray free-electron lasers, which promise to give protein structures without crystals (Physics Today, January '07). CARS spectroscopy (Coherent Anti-Stokes Raman Scattering; Spectroscopy, September '06), giving two-dimensional spectral images, to image lipid rafts and to provide fluorescence-probe-like experiments without the need for the fluorescent probes. Diffraction-grating-based laser optical methods that can provide whole matrices of traps, rather than single traps, for measuring the mechanical properties of cells, possibly relevant to cancer (Physics World, October '05). Big-physics instruments that could “see” single protein structures and real-time dynamics in solution, to learn protein mechanisms of action. Methods that could reach new time scales or space scales relevant to biology. Better quantum dots, to light up biochemical reactions inside living cells. For these technologies, too, we need the basic developments first, before they will apply to biology.

(3) Theory and experiments in evolutionary biology that could lead to insights about how pathogens evolve drug resistance. New “foldameric” polymers that could adopt folded states, like proteins and RNA molecules do, as new therapeutics and biomaterials. Chromatographic methods that might ultimately separate chiral biomolecules. Studies of the nanophysics - rather than just the nanobiology - of viruses, dendrimers, motor proteins, ATPases, microtubules and filaments.

(4) Math methods to solve stochastic coupled nonlinear differential equations; they may help us understand biochemical rate equations in systems biology. Non-equilibrium statistical thermodynamics to teach us about small-numbers fluctuations in cells. Modeling how communication networks respond to attacks by hackers and viruses to teach us how to kill pathogenic organisms by attacking its biochemical networks. Mathematic treatment of robotic linkages to help us model loops in proteins, for better drug design.

(B) Anecdotes About Missed Opportunities:

(1) According to *The Scientist* (8/29/05, page 27), Pat Brown says of his invention of microarrays: “I actually proposed the idea in an NIH grant proposal that was resoundingly rejected in 1992. It got the worst priority score I’d ever seen. In fact, the study section essentially suggested that if I removed the specific aim related to development of microarrays, and a couple of other forward-looking aims, they would fund it.” In the end, microarrays became a huge innovation that has enabled much of the proteomics revolution.

(2) Yale’s Mike Snyder is quoted in *The Scientist* (10/08/04): “We couldn’t get that project funded for the life of us”, regarding his experiment in the late 1980’s using epitope-bearing transposons to tag every protein in yeast that, some say, launched functional genomics.

- (3) Lee Hood's challenges in getting his DNA sequencer funded are well-known. He has been quoted as saying that NIH was a "bitter early opponent to the Human Genome project".
- (4) Quoted in *Science*, 306, 220, (2004), Neuroscientist Erich Jarvis (now a Pioneer Awardee) says: "You learn the hard way not to send high-risk proposals to NSF or NIH because they will get dinged by reviewers. Instead, you're encouraged to tone down your proposal and request money for something you're certainly able to do". And, according to Steve McKnight: "I never even put (that idea) in a proposal because the chances of getting an RO1 would have been zero. It's a new and unpopular idea and has no sex appeal – metabolism is boring – but I think it's pretty important."
- (5) Prominent biophysicist Charles Cantor was never able to get NIH funding to develop mass spectrometry for single nucleotide polymorphisms for genotyping. It was regarded as too risky, too expensive, and too physical. He left academia and founded the company Sequenom. Because he succeeded with Sequenom, this might be regarded as a success of the NIH system, but it raises two concerns. First, it says that the US venture capital community is willing to take more risks than our federal research agencies, inverting the classic ivory tower. To us, it indicates, instead, a breakdown in the founding principle that the federal government should fund research that is too risky and upstream of commercial applications. Second, good people will usually find ways to succeed. (However, our perception is that this is somewhat skewed by the fact that the good people who have succeeded in spite of flaws in the system are much more visible than good people who have failed because of flaws in the system. What we do know is that fewer of our best young people are opting for scientific careers than in years past. How much of this phenomenon is due to the perceptions of the young about the problems in our system of supporting research?) Our view is that NIH should support deeper innovation, not drive people to seek alternatives.
- (6) NIH rejected a 2007 application from John Miao, Professor of Physics at UCLA for 3D imaging of cells using a new method called x-ray diffraction microscopy, even though, in the study section's words, it is "capable of imaging whole cells and resolving details on the order of 10 nm and is potentially very exciting and could have an important impact in several scientific areas"; "from published work, the images are clearly better than existing methods"; "outstanding and multi-disciplinary team of investigators". The reasons for rejection were "lack of detail"; the need for "higher quality images" (despite the study section's comment that it is already "better than existing methods"); and not enough evidence yet of its advantages in biological samples. It was not even scored.
- (7) NIH rejected an application from Gordon Tollin and Victor Hruby, both Regents Professors at Arizona, to develop plasmon-waveguide resonance (PWR) spectroscopy to access new properties, not currently measurable, of lipid rafts and membrane-protein interactions. The reviewers recognized the innovation and importance of the method they invented in general, but rejected the grant 3 times because the authors had not yet proven it would give insights in the biological context.
- (8) The field of computational biology uses "forcefields", which are models of physical interactions that are used to compute the noncovalent interactions in the binding of proteins to ligands or other proteins. They are heavily used in drug discovery. Most prominent forcefield developers, including Peter Kollman and Arnie Hagler, received NIH support only to apply the existing (poor) forcefields to biological problems, not to improve the physics enough to make them successful, because study sections regarded fixing the foundations as reaching too deeply into basic physics for NIH.

(9) The Biophysical Society holds sessions, organized by NIGMS called “How to get an NIH grant”. A few years ago, one question raised from a member of the audience resonated so much with the crowd, several hundred strong, that he was the only questioner who received spontaneous applause. His question: “I am a physicist, and I wonder why I need to have already done all the research before I can apply for an NIH grant?” Certainly, some of the NIH portfolio must be incremental steps forward, but surely not all of it.

(10) Chemist Pete Schultz was unable to get NIH funding to develop autocatalytic antibodies.

(11) Commonly, NIH-funded senior investigators we asked say that they can only do the bread-and-butter research written into their RO1 grants, and for which they have preliminary data. You can “bootleg” only so much deep innovation on your RO1 grant. You can’t bootleg big ideas; otherwise you won’t make enough progress to get renewed on the next cycle. We need a mechanism that lets some of our best investigators follow grander visions to bigger-impact science.

(12) NSF funds Supercomputing Centers for all sciences. However, the NSF Medium Resource and Large Resource Allocation Committees (MRAC & LRAC) have recently voted to cap NIH-supported research at 10% (from probably about 30% currently). This poses a serious and immediate danger to the NIH-supported computational biology community, and is an example of a problem of silo funding. Physical scientists and life scientists need to be partners, not antagonists, in access to high performance computing.

(13) Below is a transcript of a conversation between Chris Miller of Brandeis and Rod MacKinnon, Nobel Laureate for his work in determining the structure of voltage-gated ion channels. MacKinnon is saying that he could not obtain NIH funding to do his channel crystallization work for which he ultimately got the Prize, and that he left Harvard for Rockefeller so that he could use his start-up money for this venture. This conversation took place in 1999, after MacKinnon had solved his first K channel structure and on the occasion of his receipt of the Lasker award. However the slow rate at which membrane proteins have been solved in the intervening years provides evidence that his assessment from 1999 about the problems with obtaining funding in this area is still true in 2007.

Dr. Miller: *From where you sit, do you see more young crystallographers emerging from their post docs beginning to be willing to undertake membrane proteins or ...*

Dr. MacKinnon: *They're not pouring in, actually. They're not pouring in.*

Dr. Miller: *It's still very risky, I would think.*

Dr. MacKinnon: *No, they're not pouring in. I think they view it as quite risky. Yeah, so the number of labs doing membrane protein crystallography is still quite small, and it is still risky, and I have colleagues who are working very hard and are worried. And rightly so. Because the problems are hard. And I have to emphasize that part of the difficulty is the problems are harder than a four-year cycle of an NIH grant. They are harder than that, and it has to be recognized.*

Dr. Miller: *And most of those problems were solved in Europe where the scientists there were not under the four-year, five-year cycle.*

***Dr. MacKinnon:** In my view, there is a very good reason why those problems have been solved outside of the United States, right, because I think that people couldn't take the risk here. I guess I left one reality out in thinking about it. I talked about the reasoning for moving was creating a do or die situation, but also you know, I had to fund this effort somehow, to be plain and blunt about it. You know, I got a start up package that helped me initiate this effort, and then I was fortunate enough to become a member of the Howard Hughes Medical Institute. But yeah, I think it's very important that it be recognized that these problems take more than four years. They are solvable, but they take more than four years, and people have to be supported for longer than that.*

SUMMARY

To bring the physical and mathematical sciences more fully into the service of deep innovation in biomedical research will require a large-scale reduction of the barriers to entry; substantial and sustained support from NIH; and a recognition of the necessity and power of supporting deep basic research in the physical and mathematical sciences to find new ideas, methods, and models, beyond what can be done with current physical science.