Bioengineering: Building the Future of Biology and Medicine

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Foreword

Harold Varmus, M.D., Director, the National Institutes of Health (NIH)

Bioengineering advances the nation's health by applying engineering principles and techniques to biological problems. The rewards most obvious to the public are novel devices and drugs, but bioengineering also offers further insight into biological processes, new methods for using data from genetics, and increased ability to visualize the brain and other organs. History tells us that most of the revolutionary changes that have occurred in biology and medicine have depended on new methods that are themselves often the result of fundamental discoveries in many different fields. Thus biological problems are too complex to be solved by biologists alone; we need partners in many disciplines, including physics, mathematics, chemistry, computer sciences, and engineering.

The symposium described in this publication was a landmark event for the NIH, and it provided an opportunity to address the grand challenges in the fields of bioengineering. While the purpose was to look to the future, it also offered an opportunity to showcase past and ongoing work. A vision of the future must build on accomplishments of the past, and we had both in abundance on this occasion.

The structure of the symposium allowed the large audience to hear from visionary scientists – our plenary speakers – but also to hear from the breadth of the community. Charting a vision for the NIH in bioengineering cannot be accomplished in a vacuum or left to a few key people. There is a wealth of talent in bioengineering and our goal is to harness it, listen to it, and act on it.

I welcomed the opportunity to open this symposium and to see the NIH more fully incorporate bioengineering into our efforts to advance science and human health.

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Executive Summary

The National Institutes of Health (NIH) convened the NIH Bioengineering Symposium to investigate research opportunities and develop recommendations that will serve as underpinnings for future medical and biological advances. The Symposium's structure ensured that recommendations would address priorities across a wide range of bioengineering sciences, which would involve multiple Institutes and Centers at the NIH and Agencies of the Federal Government. Implementation of the recommendations will realize the goal of exploiting bioengineering's capacity to bring innovative concepts and approaches to research in biomedicine and health.

Bioengineering improves quality of life through its contribution to advances in science and technology related to human health. It is unique in its ability to integrate principles from a diversity of fields. It crosses the boundaries of academia, science, medicine, and industry. As such, it is uniquely positioned to impact the health of the nation. The enthusiasm and excitement generated by the symposium are important indicators of the vitality of the profession.

Boundaries are disappearing between biology and bioengineering. The creativity of interdisciplinary teams is resulting in new basic understanding, novel products and innovative technologies. This creativity and the promise for improved health of the nation led to the creation of the Bioengineering Consortium (BECON) by Dr. Harold Varmus on February 28, 1997. The Consortium, which is chaired by Dr. Wendy Baldwin, Deputy Director for Extramural Research, includes representatives from every NIH Institute and Center and has liaisons from various other Federal Agencies. BECON's focus is to identify major issues and establish small working groups to facilitate bioengineering advances. They have established a working definition of bioengineering, and their current challenges are identifying research opportunities, facilitating interinstitute cooperation, promoting transdisciplinary training and improving the quality of peer review. BECON maintains a Web site (http://www.nih.gov/grants/becon/becon.htm) to communicate these concerns both within and outside the NIH.

In keeping with BECON's broad mission of promoting interdisciplinary communication and cooperation in bioengineering research, the NIH convened a 2-day Bioengineering Symposium on February 27-28, 1998. The purposes of the Symposium were to: (1) identify grand challenges in biomedical research that can benefit from bioengineering approaches, (2) define the role of bioengineering in future advancements in biomedical research, (3) determine how to integrate bioengineering with biological research to meet these challenges, (4) showcase accomplishments of NIH-funded bioengineering researchers, (5) increase the visibility of bioengineering to the NIH intramural and extramural research communities as well as to the NIH leadership and staff, and (6) make recommendations to the NIH for areas of future investment. The response to the Symposium was outstanding. More than 750 participants, representing academia, industry, regulatory agencies, national research laboratories, and all of the NIH Institutes and Centers attended. Plenary speakers posed provocative questions for consideration by 16 panels. The primary scientific priorities and implementation strategies are provided below. A summary of the presentations and the conclusions of the panels are included in the full report.

Scientific Priorities

1. **Through a systems approach, elucidate biological principles**. Exploding information arising from molecular and genomic studies would benefit from research using a systems integrated approach, including the quantitative aspects of physical-biological interactions in space and time, in order to gain a full understanding of the rules of how living systems operate and respond. This integrative and quantitative approach, a hallmark of engineering, will elucidate new fundamental knowledge of biological principles in terms of multiple mechanisms across hierarchical scales from molecule to cell to organ to organism to whole populations.

2. **Facilitate translation from promise to performance**. Exciting health technologies can be envisioned arising from advances in basic science and engineering. Their fruition in clinical practice depends on effective translational research and dissemination into general use. The bioengineering capacity for design and research is poised to contribute to population studies, basic research, clinical trials, databases, regulatory science, products and services that will facilitate new prevention and therapeutic strategies to meet both today's and tomorrow's patient needs.

3. **Catalyze multidisciplinary teams**. The vitality of multidisciplinary teams will be instrumental in capitalizing on the bioengineering approach to synthesize and integrate information from diverse fields into focused basic and application-oriented solutions.

Implementation Strategies

1. **Establish collaborative initiatives**. Establish new collaborative programs such as Bioengineering Research Consortia, supported by multiple Institutes and Centers, combining bioengineering, bioscience, and clinical science approaches to create innovative and effective approaches to medical and biological research. Foster academic-industry partnerships.

2. **Increase emphasis on joining engineering and biology**. Explicitly increase emphasis on joining engineering and biology in fundamental research and training, e.g., redefine the mission of and rename the Institute of General Medical Sciences (and Engineering).

3. **Reimagine the bioengineering academic structure**. Reimagine the bioengineering academic structure to create an intellectual infrastructure spanning all of the educational stages (kindergarten-career). Establish pedagogical paradigms to encourage innovative teaching methods and materials. Teach engineering within the context of biology.

4. **Communicate principles**. Through an on-going dialogue between academia, industry, government (NIH, FDA, as well as local, state, and federal legislatures), and the public, communicate successes. Facilitate the communication by creating accessible, user-friendly databases of molecular, physico-chemical, and physiologic knowledge and integrative principles.

All participants shared enthusiasm for the challenges and opportunities that motivated the NIH to convene this symposium. Both patient and health care in the United States will benefit greatly from implementing the recommendations of the symposium.

Symposium Report

The National Institutes of Health sponsored the Symposium, "Bioengineering: Building the Future of Biology and Medicine," to define the contribution of bioengineering to biomedical research and determine the best ways to ensure that bioengineering talents are used to meet the NIH's goals. The symposium, which attracted more than 750 participants from academia, industry and government, convened on February 27-28, 1998 in the NIH Natcher Conference Center. Seven distinguished speakers discussed the state of research in their fields and presented their vision of the future roles of bioengineering. These plenary lectures were followed by 16 panel sessions addressing the most important areas of research opportunity. In the panel sessions, 140 eminent scientists and engineers presented individual observations and elicited suggestions from the symposium participants. Each panel was asked to identify goals and obstacles and to prepare recommendations for new scientific initiatives of highest priority, accompanied by strategies for achieving proposed objectives. This report summarizes the presentations and outcomes of the panel deliberations. Each panel prepared a report in its own style. The results reflect the breadth and diversity of the field of bioengineering.

Overview of Presentations

Keynote Address
Senator Bill Frist, M.D. (R-Tennessee)

Dr. Frist, a heart and lung transplant surgeon who participated in the development of heart valves and cardiac assist devices, is the only physician currently serving in the United States Senate. He is chairman of the Senate Subcommittee on Public Health and Safety and the Subcommittee on Science, Technology, and Space.

Examples of bioengineering applications that have benefited patients include: (1) the use of functional magnetic resonance imaging (fMRI) that employs computer algorithms to produce detailed cardiac images without the need for invasive diagnostic procedures, (2) computerized electrocardiograms that allow the diagnosis and treatment of cardiac arrhythmias without open-heart surgery, and (3) the application of materials, microprocessors, and computer and battery technologies, which were used to develop cardiac pacemakers and a tremor control device. Bioengineering has directly benefited the health and quality of life of Americans.

Bill S.1030, the National Center for Bioengineering Research Act, would establish a Center for Bioengineering Research at the NIH. This Center would coordinate bioengineering research at the NIH and throughout the Federal Government, identify promising research areas, convene annual meetings, and allocate funds for training and research. The proposed legislation is based on a recommendation in a 1995 NIH Report, "Support for Bioengineering Research," which was requested by the Senate Committee on Labor and Human Resources. In addition, the Science, Technology, and Space Subcommittee has requested a $10 million study to define how Congress can better prioritize health research needs.

Imaging and Measurements from the Molecule to Function
Scott E. Fraser, Ph.D., Anna L. Rosen Professor and Director, Biology Imaging Center, Beckman Institute, California Institute of Technology

New biological imaging techniques permit visualization of the developing brain in intact embryos. These techniques include ways to label cells, process images at a molecular scale, visualize how cells interact, and study intercellular signals and gene regulatory mechanisms that have been proposed based on cell culture and molecular biology studies. In some cases, the new techniques have yielded information that has proved many old ideas about neural development to be incorrect. The techniques permit microscopic visualization to increasing depths but offer different compromises in terms of ease of use, performance, and price. In increasing order of cost, the techniques include the following:

- Videomicroscopy, involving a conventional light microscope equipped with a video camera and a computer-based image, permits structures as small as single microtubules to be visualized in living cells. Fluorescence energy transfer labeling techniques are used to introduce indicator dyes into single precursor cells that can then be followed over time as the brain develops. Videomicroscopy is relatively inexpensive, but can image only surface cells.
- Laser scanning confocal microscopy rejects image-degrading scattered light and can optically section thick specimens. It offers higher resolution than does a conventional microscope, but is phototoxic. Images from many planes must be collected to construct three-dimensional images.
- Two-photon laser scanning microscopy can provide good three-dimensional images of labeled cells, can see deeper (500 μm) into a specimen, and is less phototoxic.
- Three-dimensional MRI microscopy provides factors of 10^8 improvement in resolution over standard MRI and eliminates phototoxicity, but it is expensive and slow.

Processing data with computers is providing better signal-to-noise ratios, and current research is developing a functional MRI agent to enhance signals. The goal is to develop imaging techniques that permit single-cell resolution studies at the cellular/subcellular level and in the millisecond range.

Materials for Understanding and Controlling Biological Processes
Buddy Ratner, Ph.D., Professor, Center for Bioengineering, University of Washington

Biomaterials have saved lives and improved the quality of life through the use of products such as hip prostheses, vascular grafts, heart valves, percutaneous devices, stimulating electrodes, catheters, dental implants, and breast implants. However, drawbacks to each of these result from biocompatibility issues. Synthetic materials used in these devices elicit a nonspecific response, and healing results in the implant becoming encapsulated. Healing is affected by both adsorption of proteins at the surface and macrophage "interrogates." Almost all implants heal indistinguishably *in vivo*; one might hypothesize that biomaterials all absorb proteins nonspecifically, but such nonspecific protein adsorption does not occur in normal biology.

The potential exists to engineer surfaces, using patterned arrays of oriented receptor molecules, to control biological reactions to synthetic materials. A goal is to develop "stealth" materials that produce no biological reaction and will not lead to encapsulation. Such materials include polyethylene oxide, which resists protein pickup; hydroxyapatite, which heals with no capsule; certain porous materials; and artificial crystalline materials that "knock out" the inflammatory process.

High points in the evolution of precision biomaterials include the concept of molecular recognition (which led to the 1987 Nobel Prize) and the concept of cell control via receptor biology and mechanics/geometry. But the science has gone as far as it can go with conventional biomaterials. The biomaterials of the future will be engineered to be

recognized by the body as a normal part of its physiology and to precisely trigger healing. What are needed are design rules, precision controls, and education in how to use new tools to study biomaterials. Future research will focus on receptor/recognition interactions, cell-to-cell signaling, molecules in defined orientations at the cell surface, bland noninteractive regions, and molecular self-assembly.

Functional Genomics – From the Molecule to Function
Leroy E. Hood, M.D., Ph.D., The Gates Professor and Chair, Department of Molecular Biotechnology, University of Washington School of Medicine

Global tools for the analysis of biological systems and networks are needed. The following six paradigm shifts will change biology and medicine within the next 6 to 10 years:

- **Biology as an information science.** Three types of biological information will need to be deciphered: (1) chromosomes (determining DNA sequences and extracting meaning; studying genes and control regions); (2) proteins (determining structure and correlating with function); and (3) complex biological systems and networks (identifying elements and connections; determining function and emergent properties).
- **The analysis of systems and networks**. This will involve studying elements, linkages, and systems properties. Systems are complicated, consisting of subsystems, parallel information pathways, and bottlenecks.
- **High-throughput (global) tools for analysis of genes and proteins require two keys to systems analysis: databases of information and assay systems.** Tools to study genes include large-scale DNA sequencing, genotyping, DNA arrays, DNA chips, expression mapping, and identification of polymorphisms. Tools to study proteins include mass spectrometry, gel electrophoresis, and ways to predict protein folding. Tools to study cells include high-speed multiparameter cell sorting, computational biology, microfluidics, and microfabrication.
- **Common origins of all biological information means that model organisms are critical to decipher information pathways and biological complexity.** Model organisms, both simple and complex, are the "Rosetta Stones" for translating information pathways.
- **Computer science and applications mathematics will play a critical role in helping to decipher biological complexity**. Computational biology allows bioengineers to extract, store, and analyze information.
- **A systems approach to disease is revolutionizing medicine**. The global tools of genomics and proteomics offer new approaches to the stratification of disease. For example, in the case of prostate cancer, DNA arrays are being used to distinguish normal from cancer cells, which can then be used as potential diagnostic tools and as markers to evaluate therapeutic approaches. After genotype analysis, stratification can identify genetic determinants and clinical features. Once genes that predispose to prostate cancer are identified, bioengineers can decide which part of the information pathway to manipulate to prevent the disease.

Informatics – Now and Beyond
Patricia F. Brennan, R.N., Ph.D., Lillian S. Moehlman Bascom Professor, School of Nursing and College of Engineering, University of Wisconsin-Madison

The foundations of health informatics include clinical and basic biomedical sciences, computer and information science, cognitive science, public health science,

organizational science, and decision science. Parameters of health informatics include computer-based patient records, knowledge at the point of care, imaging, and telemedicine.

The following activities are on the horizon:

- Integration of different data types, with emphasis on time-variant data,
- Integration of agents and meta-data that support use of knowledge,
- Merging of public health and personal health data, and
- Reengineering of clinical practice to capitalize on information advances.

Yet, the following activities will still need to be accomplished:

- Scalable, portable applications,
- Integration of health information technologies into the clinician's work life,
- Policies and regulations supporting privacy while enhancing access, and
- Tools that support "smart" patients.

A big challenge is Translational Research, or the marriage between basic science discoveries and clinical practice. Health Informatics must help patients—such as those with precancerous conditions—make decisions; it can help accelerate the movement from bench to bedside, fostering rapid synthesis of research evidence and clinical data at the point of care. Health Informatics can provide support in following three areas:

- Basic research - The vocabulary of pictures; knowledge resources; access to distributed resources; and research workstations and networks.
- Clinical - Common terms and data models; participant recruitment; research registries and data repositories; and virtual reality environments.
- Health Services - Organized, accessible clinical data; common terms and standard definitions; intervention infrastructures; and guidelines delivered to the point of care.

Investments that need to be made include infrastructure development, informatics applications, and integrated training programs.

Delivery of Molecular and Cellular Therapies

Rakesh K. Jain, Ph.D., Andrew Werk Cook Professor of Tumor Biology, Massachusetts General Hospital and Harvard Medical School.

Malignant diseases cause about one-fourth of all deaths in the United States. The cause of death usually is metastatic disease that is distant from the primary tumor, although uncontrolled primary (or regional) tumors also are fatal to a significant number of patients. Metastases are treated systemically with chemical and biological agents, but these attempts often fail.

New strategies, collectively referred to as "molecular medicine," are thought to have the potential to be dramatically more effective. Newer agents include monoclonal antibodies, cytokines, antisense oligonucleotides, gene-targeting vectors, and genetically engineered cells. Because of their potent effects on cancer cells *in vitro* and in some tumor cells *in vivo*, these agents have been heralded as breakthrough drugs and "magic bullets" and have been accepted enthusiastically by policymakers, investors, and the general public. However, clinical results have not met the high expectations drawn from carefully planned and performed preclinical studies.

No single factor explains these disappointing results. Nevertheless, one problem requiring careful scrutiny is the quantitative understanding of the barriers to the delivery of molecular and cellular therapeutics. A blood-borne therapeutic agent (a molecule, particle, or cell) must make its way into blood vessels of the tumor, across the vessel wall into the interstitium, and to the cancer cells. Tumors develop in anatomical and physiological ways that hinder an agent at each step. In some cases, even after an agent has reached the target in the tumor, the microenvironment may reduce the agent's effectiveness.

Bioengineering approaches can analyze experimentally and theoretically each of the steps for delivery and the relationships between agent and local microenvironment. They can then integrate resulting information in a unified framework—a multidisciplinary strategy for analysis and synthesis unique to bioengineering. This approach is expected to lead to better understanding of the physiological characteristics that determine resistance to delivery in solid tumors. It also will facilitate development of novel strategies to exploit and overcome this resistance for improved cancer detection and treatment. This knowledge would allow scale-up of biodistribution of novel therapeutics from mice to humans.

Next Generation Devices and Methodologies
O. Howard Frazier, M.D., Chief, Cardiopulmonary Transplantation, and Director, Cardiovascular Research Lab, Texas Heart Institute

Since the 1960s, investigators have been working to develop mechanical devices that can assist or replace the natural heart. The program to develop a long-term implantable left ventricular assist device (LVAD) has become a paradigm for the treatment of disease. It has focused on solving a major health problem, severe heart failure, by bringing together researchers from various disciplines, including engineering, biology, biomaterials, and medicine. The LVADs of the 1970s were too bulky and cumbersome to offer a high quality of life. Therefore, in the 1980s and 1990s, development focused on device miniaturization and improved energy sources.

The ideal circulatory device continues to be elusive. Such a device would be physiologically responsive, anatomically compatible, reliable, easy to implant, and economical. In the continuing quest for such a device, researchers have produced a number of innovative LVADs: impeller, axial-flow, and centrifugal-force pumps for producing continuous flow, and internal muscle-powered pumps for producing pulsatile cardiac assistance. Out of the current generation of devices will eventually come a pump that meets the physiologic needs of patients with varying degrees of heart failure.

As new knowledge has become available, related efforts have joined the paradigm, enhancing the LVAD program. For example, early observations suggested that it might be possible to reverse induced apoptosis (programmed cell death) by allowing the heart to rest with the support of an assist device. Although rudimentary, the current understanding of apoptosis will increase as investigators continue to study the molecular basis of heart disease. When transplant immunology is better understood, fetal cell transfer and subsequent genetic remodeling of the failed heart may also be possible. Someday, molecular nanotechnology (using particles less than 1 micron in diameter) will allow "intelligent" implantable micromachines to directly modify the human body, blurring the boundary between biological and mechanical systems.

Nobel Peace Prize Awardee

The Symposium recognized the participation of fellow bioengineer, Professor Maciej Nalecz, who, with the other international officers, accepted the 1995 Nobel Peace Prize on behalf of the Pugwash Conferences on Science and World Affairs. Professor Nalecz is the Director of the Biomedical Engineering Institute of Warsaw, Poland. For 25 years he chaired the prestigious International Pugwash Council. The conferences derived their name from Pugwash, Nova Scotia, where in 1957, eminent scientists met to address the threat of nuclear war. The stimulus for the gathering was a manifesto issued in 1955 by Bertrand Russell, Albert Einstein, and other notables figures. The Pugwash Council contributed to laying the groundwork for a number of arms treaties including the Partial Test Ban Treaty of 1963, the Nuclear Non-Proliferation Treaty of 1968, the Anti-Ballistic Missile Treaty of 1972, the Biological Weapons Convention of 1972, and the 1992 Global Chemical Weapons Convention.

Beyond Informatics: The Future of Computation

Chairs: Janan T. Eppig, Ph.D., and Bernard O. Palsson, Ph.D.

The complexity and amount of biological information are increasing dramatically. New approaches will be needed to analyze and integrate this information.

Vision Statement

Bioinformatic databases must be transformed into functional models of cell and tissue processes. Accomplishing this requires harnessing the knowledge of all relevant disciplines, including computer science, mathematics, bioengineering, and biological sciences. The models will range from empirical correlations of databases to mechanistic and systemic descriptions of complex biological processes. Comprehensive informatic-based descriptions of model organisms and organs need to be developed and tested in concert with basic biological research to uncover the rules of nonlinear cellular and systemic regulation. Algorithms and other computational tools for predicting and exploring intrinsic and emergent properties of these modeled processes will be needed.

Goals for the Next 5–10 Years

- Support cross-disciplinary collaborations that hold promise for (1) developing better understanding of complex biological regulation, (2) modeling complex systems coupled with experimental validation, and (3) developing mathematics and software tools for discovering emergent properties of biological systems.
- Develop database and software infrastructure standards.
- Seek improved definition, interpretation, and analysis of sequence data, including development of automated annotation methods and better algorithms.
- Develop methods for visualizing and interpreting large and possibly heterogeneous data sets and the results of multivariate, time-dependent simulations of biological and biomolecular systems.
- Move beyond sequence data to incorporate metabolic pathways, genetic circuits, and cell, tissue, and organ function into models.
- Translate empirical data into concepts that can be applied to the development of therapeutic, metabolic, tissue, organ, and prosthetic device engineering and design.
- Develop new tools that are predictive of complex biological properties, i.e., redundancy characteristics, emergent properties, and evolutionary dynamics.
- Design experiments to build mesoscopic databases, including those describing the physico-chemical properties of gene products and databases on physiological function.
- Develop genome-based organism-scale models for the analysis, interpretation, and prediction of the genotype-phenotype relationship.
- Establish bioengineering as the home for interdisciplinary educational programs and courses (bioinformatics, biomedical modeling, and computing).
- Develop a funding infrastructure that allows science and technology to be developed simultaneously and allows for methods- and development-driven research.

Barriers and Solutions

Barrier: Multidisciplinary training is rare and it is hard to integrate computer science, biology, and engineering in one place. Solution: Establish bioengineering as the home for interdisciplinary (bioinformatics, biomedical modeling, and computing) educational programs and courses – because it is new, rapidly evolving, and placed at the interface of biology and engineering, and because existing curricula already contain many of the fundamental courses.

Barrier: Multidisciplinary interactions are difficult. Solution: Establish funding programs and priorities at the NIH that recognize the need for interdisciplinary research. In particular, the need for methods- and development-driven research has to be recognized. Establish a Science and Technology Center program for bioinformatics, genome sciences, and bioengineering. Also, permit linked smaller-scale grants.

Barrier: Functional models based on current bioinformatic databases are difficult to build. Solution: Develop infrastructure for the description of the: (1) physico-chemical properties of gene products and (2) simultaneous function of multiple gene products.

Barrier: Databases for physico-chemical properties of gene products and for integrated physiological function are lacking, in contrast to the growing genomic and proteomic databases. Solution: Design experiments and database structures to build databases for relevant physico-chemical and physiologic data and to integrate these databases with the rest of the bioinformatics infrastructure.

Barrier: In the past, model-building in biology has been abstract. Solution: Develop knowledge-based modeling for validation and testing. For cell modeling, use a regulatory data/code system-subsystem approach. Couple tools for computational model-building with experimental validation studies.

Scientific Priorities

1. **Emphasize basic research for discovering the rules of biology**, particularly through comparative genomics and understanding the nonlinear aspects of cellular processes and biological regulation.
2. **Develop database and software infrastructure standards** that support the access, creation, and analysis of biological and biomolecular data and its translation into functional models. Develop an infrastructure that allows for the formulation, analysis, and testing of functional models and experimental testing and validation of predictive functional models.
3. **Develop computer-based models of well characterized biological organisms**. These models should describe the complete molecular, biochemical, cellular, and developmental functions of the organisms and integrate basic knowledge with a systems approach.

Implementation Strategies

- Recognize formally within the NIH structure the need for systems and computational research and development resulting from bioinformatics and genomics. This effort should span software development, elucidation of the physico-chemical properties of gene products, formulation of functional models of living processes, and discovery of emergent properties and biological rules.
- Immediately establish a funding infrastructure that allows for the simultaneous development of science and technology in bioinformatics, genome sciences, and bioengineering. A Science and Technology Center funding model should be considered, with more than one size/funding level.
- Initiate new educational and training opportunities and build the associated infrastructure.
- Form initiatives to build organism-scale functional models for selected model organisms for which the needed bioinformatics and genomic data are available.

Bioelectric/Biomagnetic Phenomena: Ion Channels to Organ Function

Chairs: David B. Geselowitz, Ph.D., and Jose Jalife, M.D.

Many patients benefit annually from the use of devices or other treatments aimed at the diagnosis and treatment of diseases, such as sudden cardiac death and stroke, for which electrical abnormality in the tissue is an important component. However, such approaches are primarily empirical and, other than being able to say, "they sometimes work," a rational basis for their use is still lacking. As a result, these diseases remain among the major killers in the United States and elsewhere. A precise quantitative understanding of such diseases is a major challenge faced by clinicians, as well as basic biologists and bioengineers. Achieving that understanding would have significant health benefits and should be a major priority in science and technology.

Vision Statement

Diseases involving electrical dysfunction in the heart, brain, and skeletal muscles are major health problems. Future advances may depend on improved methods for detection of electric and magnetic signals, innovative combining of bioelectric phenomena with chemical, acoustic, optic, and motion information, and development of mathematics to analyze more accurately nonlinear processes. The technology-development and integrative systems skills of biomedical engineers will play a major role in future studies of bioelectric and biomagnetic phenomena, including applications to diagnosis and therapy.

Goals for the Next 5–10 Years

- Develop advanced experimental and computational tools, techniques of signal analysis and processing, and models to enable integration of understanding of molecular mechanisms of ion channel behavior and structure/function of cells with knowledge about global mechanisms of tissue/organ function, including the complex dynamics of excitation and electrical wave propagation in excitable media.
- Combine images of bioelectric phenomena with functional and anatomic images from other modalities to aid in diagnosis and therapy.

Scientific Priorities

1. **Improve understanding of mechanisms and dynamics of nonlinear bioelectrical phenomena** from the molecule to the organ level through development of advanced experimental and analytical tools.

2. **Develop advanced computational tools and models** to enable integration of understanding of molecular mechanisms of ion channel behavior and structure/function of cells with knowledge about global mechanisms of tissue/organ function, including the complex dynamics of excitation and electrical wave propagation in excitable media.

3. **Develop noninvasive techniques** to identify individuals at risk for electrical diseases and to identify and treat individuals who have experienced an event outside the hospital.

Implementation Strategy

The panel recommends the development of inter-Institute multidisciplinary research and training programs focusing on technology-directed and hypothesis-driven issues of bioelectrical phenomena, from the molecule to the patient. One possible model is the program for Specialized Centers of Research supported by some NIH Institutes. Centers for Specialized Research in bioelectric/biomagnetic phenomena could include biomedical engineers as well as experimental and theoretical biologists, physicists, and clinicians working together toward a common theme related to bioelectrical diseases. The goals of such centers should include, but not be limited to, those stated above.

Bioengineering in Clinical Medicine

Chairs: William R. Hendee, Ph.D., and Willa A. Hsueh, M.D.

A large portion of scientific research supported by the NIH can be described as hypothesis-driven, basic research. This research provides the ideas and knowledge for advances in treatment and medical care. At the other extreme, clinical trials are an essential step in moving from a preliminary demonstration of a treatment to a documented safe and effective treatment. Translational research focuses on the research that goes on between those ends.

Vision Statement

Improvements in preventive, diagnostic, and therapeutic medicine require the ongoing infusion of new technologies (drugs, devices, equipment, and procedures) evolving from discovery and knowledge gained through basic biomedical research. In turn, challenges in clinical medicine help focus basic research efforts on the search for improved ways to meet clinical needs. The dual-pathway migration of knowledge between basic research and clinical evaluation and use is defined as translational research. Nurturing this migration to stimulate productive research and improve clinical medicine is an ever-present challenge for the NIH. Today this challenge is accentuated by external forces such as managed care and a regulatory environment.

Scientific Priorities

1. **Develop and document models of translational research.** Models of successful translational research can increase recognition of it as an essential component in enhancing productivity in basic biomedical research and clinical medicine. Models should emphasize the following dual pathways: the development of new technologies for clinical medicine and the role of clinical medicine in guiding fundamental research. An example of the path from basic research to clinical medicine is the evolution of imaging technologies such as transmission-computed tomography and magnetic resonance imaging. An example of the reverse path is how the clinical need for artificial organs influences basic research in immunology and biocompatibility. Models such as these need to be documented in detail to illustrate the importance of translational research in the two-way path between the laboratory bench and the patient bedside. NIH resources are needed to conduct retrospective and prospective models of successful and unsuccessful translational research.

2. **Provide incentives for translational research.** Translational research requires the cooperation of basic and clinical scientists to facilitate the two-way transfer of knowledge between bench and bedside. This requirement demands teams of experts, rather than solitary investigators, to perform research. Each expert must have enough interdisciplinary knowledge to be able to communicate effectively with other team members and enough skill to contribute productively to the research. Developing such experts goes beyond traditional training programs, even training in disciplines such as bioengineering, which is multidisciplinary in scope. Resources for developing new educational approaches include directed support programs from the NIH. Incentives in academic institutions are needed to attract persons committed to translational research, as are changes in the institutional reward system to recognize the value of translational research and those engaged in it. In the development of educational programs for translational researchers, the opinions and suggestions of

industry leaders should be solicited. These leaders should contribute to the design and support of the programs.

3. **Direct resources toward translational research.** Translational and clinical research endeavors historically have been funded by three sources: clinical revenues, industry, and the NIH. Managed care is decreasing the availability of funds from the first two sources, and over the past few years support from the NIH has been directed increasingly toward molecular and genetic research and away from translational and clinical research. These trends place translational research, and its ultimate contributions to improved patient care, at substantial risk. To address this growing problem, the NIH should consider funding programs that specifically support translational research. These programs might be modeled after programs currently in existence, such as those targeting small businesses, although access to the programs should not be restricted to specific types of organizations.

Implementation Strategies

- **Recognition**. The NIH should recognize that an increased focus on translational research as an integrative, multidisciplinary process is essential to the ongoing productivity of basic biomedical research and advanced clinical medicine.

- **New Models**. The NIH should assist in the development of successful models of translational research as paradigms for the collaboration of academia, industry, and Federal agencies in the migration of knowledge in support of basic research and clinical medicine.

- **Intellectual Infrastructure**. The NIH should help support new approaches to educate persons committed to translational research, including bioengineers, mathematicians, information technologists, statisticians, biologists, chemists, and research-oriented physicians, to create the intellectual infrastructure necessary for productive translational research.

- **New Programs**. The NIH should recognize the value of translational research by creating new programs supporting translational research.

- **Role of Bioengineering**. The NIH should identify bioengineering as a logical focal point for convergence of needs and resources for translational research.

Bioengineering: Education and Training

Chairs: Martha L. Gray, Ph.D., and Larry V. McIntire, Ph.D.

To effectively explore the potential for bioengineering approaches to advance biomedical research, scientific leaders must anticipate the necessary skills investigators will need in order to address future research challenges.

Vision Statement

In recent years, understanding of the fundamental mechanisms of disease has improved enormously, with commensurate changes in the practice of medicine. These changes have driven an exponential growth in the potential for engineering to contribute to medicine through increased biomedical understanding, innovative diagnostics and therapeutics, and improved health care delivery. For this potential to be realized, however, there is a need to focus on the educational infrastructure expected to produce the biomedical engineering leaders of the next century.

In considering the educational infrastructure, *interdisciplinary* and *integrated* are key words that emerge from any perspective. From the perspective of career paths, biomedical engineering education must provide a foundation for industry, academic science, and medicine. Each path provides enormous opportunities to improve the social, economic, and health status of the United States. A cadre of bioengineers is necessary to translate the country's lead in biomedical science into industrial opportunities and economic development, to increase the scope and speed of scientific advances in biomedical science, and to bring an increased analytical perspective to the practice of medicine.

From the disciplinary perspective, many problems in medical science respond only to the combined contributions of engineering, science, and medicine. Thus, the educational infrastructure must provide a mechanism for students to integrate across multiple disciplines.

From a more general perspective, biomedical engineers must be able to adapt to a changing science base and to the internationalization of the work place and must be able to appreciate the ethical and political implications of research.

As the number of educational programs begins to grow in response to these opportunities, bioengineers have focused intensely on – and led the way in – establishing innovative organizational structures and teaching paradigms for integrated, interdisciplinary education.

Goals for the Next 5–10 Years

- Identify a core curriculum for bioengineering.
- Develop training strategies appropriate to the differing career paths of bioengineering graduates in industry, academic science, and medicine.
- Find the best academic structures and teaching paradigms to generate bioengineers who can adapt to changing science bases and internationalization of the workplace and can appreciate the ethical and political implications of research.

Scientific Priorities

1. **Develop strategies to lower the barriers that naturally arise at institutional and disciplinary interfaces.** At most institutions, the current educational infrastructure in engineering (and in other areas) is department-dependent. With the increased recognition of bioengineering as an emerging discipline, bioengineering departments

are being established at many universities. This development enhances educational opportunities, but it also raises concern about barriers that often isolate departments. It is necessary for bioengineering students to maintain strong links with engineering and the life sciences. Students in traditional departments must have the opportunity to learn the language of complementary disciplines. Understanding the differences between academic and industrial cultures is also essential.

2. **Establish new pedagogical paradigms and innovative teaching methods**, including effective use of the latest computer-based approaches. Bioengineering requires the ability to use engineering approaches to examine complex biological systems spanning the length scale from molecules to organs. With few exceptions, the pedagogical approach involves the student or teacher integrating material from "traditional" engineering (mechanical, electrical, chemical, etc.) subjects and applying it to biological problems. The panel agreed that the lack of pedagogical tools is a major barrier to effective biomedical engineering education.

3. **Increase the level of quantitative skills at all levels (K-career).** Biomedical engineering requires a rigorous mathematics training and ability to think in an analytic manner. The panel felt strongly that this recommendation is a life-long learning issue that must be addressed as early as elementary school.

4. **Raise public awareness** (in the general, medical and industrial communities) of the importance of biomedical engineering in medical breakthroughs. Communicating the skills and power of an integrative systems approach to research and development is a principal challenge. The persistent perception that biomedical engineers build instruments as directed and used by physicians poses a barrier to the effective involvement of biomedical engineers in advancing medicine and the medical industry.

Implementation Strategies

To address these recommendations, the NIH should develop new training and educational initiatives to foster innovative bioengineering teaching programs. Individual NIH Institutes are encouraged to join forces so that multi-Institute bioengineering training grants can be established, thereby diminishing the obligatory constraints of a single Institute and allowing for support of a critical mass of students. In addition, the NIH is encouraged to establish a reasonable number of focused biomedical engineering centers, each of which integrates education, training, academic research, and industrial applications in an area crucial for development of 21st century medical treatments. These centers might be modeled after the Engineering Research Centers and the Science and Technology Centers of the National Science Foundation.

The panel identified two critical elements for addressing all of the recommendations. The first is to encourage flexibility and experimentation with respect to organizational and educational structures, so as to maximize the potential for continued innovation in teaching, cultivation of industrial ties, and expansion in public awareness. The second critical element is to have a better coordination of efforts and initiatives among agencies engaged in supporting biomedical engineering (NIH, NSF, DOD, Whitaker Foundation, etc.). A well coordinated alliance among agencies provides an unparalleled opportunity and powerful incentive to deploy resources to build a solid educational infrastructure – one that requires educational development, as well as student and research support.

Biomechanical Solutions

Chairs: Yuan-Cheng Fung, Ph.D., and Carol L. Lucas, Ph.D., M.S.

Biomechanics is a branch of engineering science dealing with the roles of force, deformation, and motion in living organisms. The field has made important contributions over the years to understanding human physiology and pathology and to the development of advanced medical diagnostic and treatment procedures, processes and products. The continued application of biomechanics combined with other bioscience disciplines will lead to further innovation and advances in stategies for improving health. Future directions include the biomechanics of biomolecules, DNA, genes, genetic circuits, cells, extracellular matrix and tissues, and the integration of molecular biomechanics with the physiology of organs and the whole individual.

Vision Statement

Biomechanics is a branch of engineering science dealing with force, deformation, and motion in biology, from molecules to whole individuals. Biomechanics impacts every area of medical disease. No disease will ever be fully understood unless it undergoes a complete stress analysis. All cells in the body – stem cells, endothelial cells, embryonic cells, etc. – are strongly affected by the geometry and stress factors in their environment, factors that influence key functions such as gene expression, growth, and development.

Biomechanics has contributed to understanding physiology and pathology, development of medical diagnostic and treatment procedures, design and manufacture of prostheses, improvement of human performance in workplace and sports and automobile safety, injury prevention, and protection of the aged, handicapped, sick and injured. Biomechanics has addressed problems of blood circulation, musculoskeletal systems, ultrasound imaging, tissue remodeling, mass transport in kidney dialysis and in cancer drug delivery, development of artificial internal organs and joints, automated gait analysis, human tolerance, and tissue engineering. It is relevant to treatment strategies for many diseases, from gene therapy to surgery.

In vigorous development for the future are the biomechanics of biomolecules, DNA, genes, genetic circuits, cells, extracellular matrix and tissues, and the integration of molecular biomechanics with the physiology of the organs and the whole individual. As an engineering discipline, biomechanics is uniquely qualified to address these broad issues. Biomechanics must be an integral part of a solution to the grand challenge of integrating bioengineering with biological research of the next 1-2 decades.

Scientific Priorities

Provide incentives to foster cooperation among biomechanicians, biologists and physicians in the following high impact areas:

1. **Adaptation to stress, including repair, fatigue and failure**. All cells and tissues experience stress *in vivo,* and respond to their mechanical environment by adaptation, remodeling, and a host of subcellular and molecular events, whose normal course is essential to function and whose abnormal course can lead to failure or disease. Thus, it is important to understand the mechanics of these processes and the mechanical aspects of the entire stimulus-response cascade that translates mechanical force to molecular processes from the molecular level, through increasing sizes of scale, to observable change. Typical research areas include: remodeling arteries, bones, and other tissues; tissue responses to artificial implants and bioactive materials; remodeling

injury and healing; development of constitutive equations at multiple scales; and stress effects in differentiation and development.

2. ***In Vivo* biomechanics**. There is a need to emphasize the use of biomechanics to solve problems *in vivo*. Data on forces (stresses) and motion (strains) *in vivo* at the subcellular, organ, and whole-body levels are required to provide the basis (i.e., boundary conditions) for analysis of function. *In vivo* biomechanics includes characterization of normal states as well as the aging process at the ultrastructural, microstructural, and macrostructural levels, diagnostics of disease states, evaluation of therapeutic approaches, surgical pre-planning, treatment modalities, and outcome. Temporal changes as a result of treatment and various interaction and feedback mechanisms can also be analyzed by biomechanical methods. Along the same line, successful delivery of drugs and genes to treat diseases – such as to reach solid tumor – will need *in vivo* biomechanics. Continued improvements in the design and application of implants, prostheses, and artificial organs cannot be achieved without biomechanics. Meanwhile, new technology and measurement techniques will need to be developed for all levels of biomechanics. More sophisticated analytical tools, computational models and procedures will also be required. It is important to note that these new tools must be verified and validated before their application. Further, the methods of approach must be integrative, i.e., bridging length-scales from the subcellular level to entire physiological systems.

3. **Molecular biomechanics**. There is a need to develop molecular mechanics to understand the mechanical behavior of biomolecules, the dynamics of the interaction of molecules in cells, the pathway of force transmission from extracellular matrix through the cells, how force and deformation of the cell membrane induce forces in the nucleus to cause gene expression and production of proteins, how cells interact with each other through mechanical contacts, and how tissue formation, growth, and remodeling are influenced by molecular mechanics. Studies of the potential functions (or strain energy function) of the molecular backbone and the electron cloud surrounding the backbone may provide a foundation of the molecular mechanics approach. For example, if researchers know the function of the molecular structure of the cells as well as they understand the structural mechanics of an airplane, and if they know the forces acting on cells as well as we know the aerodynamics of the airplane, then it will be possible to design and modify the cells, tissues, and organs for biological functions. Molecular mechanics will be one of the bases of understanding physiology and pathology and will provide fundamental principles for creating tissue substitutes.

Implementation Strategy

The panel proposes that biomechanicians become more proactive, informing their colleagues in biology and medicine of the importance of biomechanics in fully understanding disease processes. In this regard, it would be useful to include awareness of the value of biomechanical input on solicitations for grant applications. In addition, small, rapidly funded grants may foster innovative interaction and permit otherwise impossible collaboration in potentially vital areas not yet fully explored.

Biomedical Engineering in Rehabilitation

Chairs: P. Hunter Peckham, Ph.D., Naomi Lynn Gerber, M.D., William Z. Rymer, Ph.D.

Nearly 50 million people in the United States have a disabling condition. Their needs range from improving their physical or mental capacities to providing access to the workplace so they can achieve a productive and satisfying life.

Vision Statement

Biomedical engineering plays a pivotal role in the rehabilitation process by assisting with restoration and substitution of functional loss. By virtue of their dual training in biology and engineering, biomedical engineers draw from the knowledge base of many of the life and physical sciences and apply this knowledge to develop meaningful applications that improve a person's body, mind, and contribution to society.

The recent Institute of Medicine report, *Enabling America*, classifies disabilities broadly into the following areas: pathophysiology, impairment, functional limitation, disability, and societal/environmental limitations. Disability emerges from the interaction between impairment and societal or environmental barriers. While many areas of science and engineering contribute to the resolution of organ system pathology and impairment, biomedical engineering is uniquely qualified to develop and implement substitutions for organ function and to reduce the adverse effects of societal and environmental barriers on the lives of disabled people. Biomedical engineers can help compensate for functional limitations and reduce the impact of societal and environmental barriers. They emphasize the overriding need to maintain and restore functional capacity to optimize quality of life.

Goals for the Next 5–10 Years

- Seek and incorporate consumer feedback into research. Disabled people often develop novel adaptive strategies, and individual reactions to disabling illnesses vary broadly. Furthermore, consumers often have priorities different from those of researchers or have concerns because they are employing a new device in a real-world setting that may not resemble the testing environment. One way to obtain consumer feedback is to use a listserve on the Internet. It is also recommended that investigators receiving NIH support be asked to briefly summarize their project in lay terms so consumers can understand and offer comment.

- Improve education and training in the field of biomedical engineering and increase general awareness of the field and its contribution to rehabilitation. Many medical care providers are not aware of the new technologies and how to use the products correctly, because their information comes from a vendor, rather than from independent sources. Many consumers are unaware of technologies that can help them and they also rely on advice of vendors and medical providers. Biomedical engineers are not routinely trained to understand the central biological or medical problem. As a consequence, researchers are often out of touch with what is needed and with the concerns of the consumers. One solution is to ensure that research is clinically driven by encouraging and rewarding clinicians to interact intensively with engineering researchers.

- Improve technology transfer. Rehabilitation frequently involves high-cost, low-volume devices that are not commercially viable without substantial initial investment. One possible solution is for the NIH to emulate the Advanced

Technology Program of the U.S. Commerce Department, where small businesses join with large companies to pool resources.

- Improve consumer access to products. Many consumers have managed care plans that do not pay for potentially valuable products. Bioengineers must build scientific evidence of efficacy to encourage managed care to pay for the products.

- Improve the scientific knowledge base for rehabilitation, drawing on biomedical engineering methodologies and techniques to assist with evaluating mechanisms and outcomes. One possible solution is to emphasize the importance of rehabilitation research within the NIH and to urge that support be provided to achieve a critical mass of rehabilitation research.

Scientific Priorities

1. Characterize and assess functional loss in chronic disabling conditions. Bioengineers need to develop a strong scientific basis for measurement of functional loss, while recognizing that human disability emerges as an outcome of the interactions between human impairment and environmental barriers or constraints. As engineers develop substitution technologies, requirements for quantifying the effects of these substitutions emerge, including the person's adaptation to the substitution technology and the ensuing interaction between the person and the environment after the substitution. To quantify these effects, it is necessary to rigorously describe the performance base of the person as well as to assess the person quantitatively in real-life situations. We must develop new measurement paradigms that allow for issues important to the consumer, such as pain, cognition, and incontinence. New measurement tools will have to be practical, simple to use, and of reasonable cost, to allow their widespread use in routine clinical settings.

2. Promote strategies to restore or substitute for functional loss. Given that rehabilitation deals primarily with chronic illness and disability (where complete restoration of organ function is usually not feasible), new engineering technologies should be developed that substitute for organ functional loss as well as restore the capacity of a person to perform optimally within his or her environment.

3. Develop strategies for the transfer of relevant knowledge from other engineering and physical sciences pertaining to substitution for or restoration of functional loss in chronic disabling conditions. Bioengineering draws from many disciplines, and bioengineers need to capture findings from these disciplines and adapt them to rehabilitation. Bioengineers need to use various engineering technologies to strengthen their base of scientific knowledge. A mechanism for obtaining and incorporating feedback to create new and refined existing products is also needed.

Implementation Strategy

In all research and training initiatives, the NIH should consider functional restoration and substitution as a venue in which biomedical engineering can contribute actively to human welfare. This contribution can occur in all phases of illness – ranging from limited objectives, such as rectifying impairment of particular organ function, to the broader issues of optimizing human interaction with the environment. Biomedical engineering must be made more central to the rehabilitation research effort. The knowledge base of effective tools, techniques and evaluation mechanisms should be expanded. These tools and techniques need to be better disseminated to consumers.

Combinatorial Approaches to Biology

Chairs: Jane V. Aldrich, Ph.D., and David H. Sherman, Ph.D.

Combinatorial chemistry and combinatorial biology-based approaches for the development of novel pharmacological agents and biomaterials have emerged as powerful long-term solutions for discovery of novel pharmaceuticals. Combinatorial chemistry strategies have been devised to efficiently generate large numbers of "combinatorial libraries" of soluble molecules, libraries of compounds tethered to resin beads, silica chips or solid supports, recombinant peptide libraries on bacteriophage and other biological display vectors. Combinatorial biology involves genetic manipulation of bacteria and fungi that produce complex natural-product chemical entities. This technology includes construction of large libraries of recombinant microbes capable of generating novel organic molecules, as well as engineering secondary-metabolite biosynthetic pathways to modify, in a highly directed fashion, valuable biologically active microbial metabolites.

Vision Statement

The panel envisions the development of generally valid paradigms and techniques based on combinatorial approaches for the design, synthesis, characterization, assay, and end-use evaluation of complex, novel molecular entities and interactions. It is expected that within 5-to-10 years, combinatorial paradigms will become an engine of innovation in a variety of fields with particular emphasis on pharmaceutical sciences and drug delivery, medical device development, and materials design and engineering.

Goals for the Next 5–10 Years

Significant opportunities and challenges for combinatorial technologies lie ahead. Significant synergies exist between combinatorial biology and chemistry and allied fields of bioengineering, genomics, and bioinformatics. The pharmaceutical industry has already adopted combinatorial methodologies as a key technology for its drug discovery effort. Indeed, several compounds discovered from combinatorial chemistry libraries have advanced to clinical trials. Success has already been evident in the combinatorial biology arena, with directed manipulation of a natural product biosynthetic pathway leading to the commercial development of an antiparasitic agent. Although these successes are evident, advancing fundamental aspects of combinatorial approaches will undoubtedly lead to more rapid discovery and efficient development of new pharmaceutical agents and advanced biomaterials for improved health of the nation.

Barriers

- Currently there is no mechanism for effectively handling grant proposals that employ multidisciplinary research.
- There is a general lack of effective networking and interaction among the combinatorial-based fields.
- There is a lack of understanding of fundamental biological properties for library design and of linkage between genomics and combinatorial approaches.
- The current complexity of assay formats limits efficient screening throughput of combinatorial libraries.

- There is need for availability of end-use assays for discovery of new molecules and biopolymers, including nanoscale miniaturization methods and biocompatibility assays.

Scientific Priorities

1. **Develop enhanced synthetic methodologies for combinatorial chemistry.** This will include both chemical and biochemical approaches and increased emphasis on polymer chemistry for supports for synthesis and design of novel templates and scaffolds. A component of this will be development of new automation and robotics tools and approaches for obtaining combinatorial libraries.

2. **Develop analysis tools that complement combinatorial approaches**, including high throughput screening, chemical analysis, and biological assay. Development of combinatorial approaches to characterize targets would be a novel application of this approach.

3. **Develop tools for information management and dissemination** to cope with the large amount of data generated by combinatorial approaches. Areas to focus on include:
   - Computing resources to handle the information and data,
   - "GeneBank"/ChemAbstracts-like databases specifically for combinatorial libraries,
   - Search tools for library structural properties,
   - Approaches for increasing interactions among tool-development computer scientists,
   - Techniques for advanced data reduction, multidimensional analysis, and pattern recognition,
   - Networking schemes to encourage formation of multidisciplinary research teams of researchers interested in combinatorial approaches.

Implementation Strategies

To address these priorities, the NIH should foster development of cross-disciplinary research and education initiatives and of funding mechanisms for centers focused on high-impact combinatorial research.

Functional Biomaterials

Chairs: Rena Bizios, Ph.D., and Peter Johnson, M.D.

A large number of Americans suffer organ and tissue loss every year from accidents, birth defects, conditions, and diseases such as cancer, diabetes, and osteoporosis. Improved understanding of biological processes holds promise for the development of new classes of biomaterials, polymers, and diagnostic and analytical reagents. New avenues of scientific inquiry can enable the development of novel tissue and organ replacement technologies that are designed to perform ideally in their respective biological environments.

Vision Statement

The panel envisions harnessing the knowledge of all relevant disciplines to design functional biomaterials (including device components) that will guide specific tissue/organ structure and function. This process will incorporate knowledge of tissue structure, material properties, cell function and protein/cell-material interaction guided by clinical relevance, ethics, and acceptable cost and manufacturing requirements.

Goals for the Next 5–10 Years

- Investigate the basic biology of wound healing.
- Correlate *in vitro* with *in vivo* responses.
- Develop standardized and quantitative cellular, genetic, and metabolic response assays/protocols, including those for accelerated biocompatibility.
- Develop noninvasive/nondestructive assays of biomaterial performance.
- Develop optimal resorbable and nonresorbable biomaterial carriers for cell and tissue induction factors.
- Explore biomaterial self-assembly in three and four dimensions.
- Incorporate clinical application requirements into the design of functional biomaterials.
- Develop parallel experimental systems wherever appropriate.
- Include assessment of manufacturing needs and cost-effectiveness in the functional biomaterials design stage.
- Clarify the educational goals for the next generation of biomaterial scientists/engineers (including clinical engineering and basic science exposure) and foster their implementation within institutions.
- Improve communication and interactions among basic scientists, clinicians, engineers, government, and industry.
- Incorporate all relevant forces and stimuli (electrical, mechanical, etc.) in the development of functional biomaterials.

Barriers and Solutions

Barrier: Limitations of current *in vitro* and *in vivo* models for the evaluation and prediction of human response to biomaterials *in situ*. Solution: Make this a scientific priority.

Barrier: Lack of adequate and appropriate quantitative methodologies for the analysis of tissue, cellular, metabolic, and genetic responses to biomaterials. Solution: Make this a scientific priority. Consider the development of centers to provide such complex analyses.

Barrier: Linear and time-consuming nature of current experimentation. Parallel experimental systems are needed. Solution: Emphasize the development of parallel

experimental methods, such as combinatorial biomaterial development and testing, that optimally leverage resources (including time).

Barrier: Poor communication of concepts among disciplines and stakeholders. Solution: Develop a standard lexicon for functional biomaterials and their applications (for example, ASTM Standards process). Generate a mechanism to support an ongoing dialogue between academia, industry, government (NIH, FDA, etc.) and the public.

Barrier: Difficulty in stimulating needed multidisciplinary interactions within and between academic institutions and industry. Solution: Explore successful models of multi-disciplinary interaction, such as virtual corporations and existing centers, and apply them where appropriate.

Barrier: Poor interdisciplinary training mechanisms. Solution: Develop a new breed of specially trained scientist-engineers (for example, bioengineers) qualified to address the development of clinically relevant functional biomaterials. This educational goal will require significant reshaping of existing institutional training mechanisms.

Barrier: Absence of a comprehensive resource for animal research. Solution: Develop such a center.

Barrier: Inhibited development of functional biomaterials because of perceived high legal and regulatory barriers that heighten corporate risk. Solution: Bring the FDA to the table. Promote the development of standards for expert legal testimony.

Barrier: Poor public understanding of issues regarding biomaterials. Solution: Incorporate public education outreach mechanisms into the overall NIH bioengineering program.

Barrier: Absence of relevant standards for functional biomaterials. Solution: Develop and establish consensus standards for functional biomaterials and their components using the existing standards development mechanisms (e.g., ASTM, ISO).

Scientific Priorities

1. **Develop *in vitro* and *in vivo* models** that are more predictive of human responses to biomaterials.
2. **Develop and apply quantitative methodologies** to monitor genetic and metabolic responses of cells/tissues to biomaterials to provide mechanistic understanding.
3. **Improve understanding of wound healing around implants**. This should incorporate an understanding of protein interaction with biomaterials so as to foster timely cell attachment, desired subsequent function, and prevention of microorganism attachment.

Implementation Strategies

The NIH should require universities to focus on engineering and emphasize the need for enhanced intra- and inter-university collaboration (including virtual collaboration) in order to engage the multiple disciplines needed to achieve progress in this field. An advisory mechanism should be constructed to include the intramural NIH, academia, and industry to refine the goals and mechanisms of bioengineering research especially as applied to functional biomaterials.

Functional Genomics from the Genome to the Physiome

Chairs: Shu Chien, M.D., Ph.D., and Ronald W. Davis, Ph.D.

Recent advances in biology, particularly by the Human Genome Project, have generated a vast amount of data on DNA sequences of the genomes of humans and other organisms. Progress has been accompanied and facilitated by the development of high-throughput analytical tools, thus creating many additional challenges and opportunities for biology and medicine. Bioengineering is in a unique position to contribute to the further development of these technologies, and to use them to integrate knowledge of genomics and hierarchical levels of living organisms. Understanding molecules, cells, tissues, organs, organisms, and communities as integrated entities is the next major frontier in biomedical sciences, and bioengineering should take the leadership in advancing this understanding.

The high-throughput analytical tools used in the analyses of the genome, proteins, and cells will be complemented by the development of other new technologies, e.g., nanotechnology, computational biology, and smart materials, forming the foundation for deciphering the network information of complex biological systems. A scientific goal is to establish, in various biological systems, the physico-chemical properties of the system components (from genes to molecules, cells, tissues, organs, and organisms) and their regulation and interaction. The technological tools should be integrated with biology, chemistry, computer science, engineering, mathematics and physics to achieve a systems science approach for the analysis of biological information. Bioengineering is central to this activity.

Genomics has demonstrated the unity of biological information in living organisms at different evolutionary levels. Many human genes have their counterparts in yeast, *Drosophila*, and mice. The function of genes can be studied in such environments, and the insights can be applied to researchers' understanding of human biology and disease. Functional genomics will aid in the identification of genes predisposing to various disease types and the stratification of disease for the optimization of preventive, diagnostic, and therapeutic strategies.

Paradigm changes in the life sciences will require remolding academic structures, including training scientists differently and forming academic consortia to tackle systems problems which demand broadly interdisciplinary approaches.

Vision Statement

Bioengineering should play a key integrative role in functional genomics, including the integration of research and education across disciplines and among academia, industry, and society. Bioengineering principles should be applied to the characterization of genetic and physico-chemical properties of components of biological systems at various levels and to the understanding of function in terms of the regulation and interaction of these components.

Goals for the Next 5–10 Years

- Create reliable databases with standardized input/output formats.
- Develop a useful functional model of a yeast cell incorporating genetic and physico-chemical data that can predict its physiological behavior in different environments.
- Develop tools for systematically comparing gene and protein functions across species.

- Foster development of model assay systems, including surrogate organs and living tissues, to evaluate gene function.
- Formulate predictive computer and *in vitro* models of components of representative mammalian systems.
- Enlarge the cadre of scientists having the interdisciplinary knowledge and skills needed to contribute optimally to functional genomics.

Barriers and Solutions

Barrier: Lack of communication between disciplines. Solution: Educate students and scientists across disciplines and minimize jargon.

Barrier: Lack of quality-controlled databases on physico-chemical properties of system components. Solution: Develop methods and technologies whose outputs incorporate validated quality metrics; require that databases include these quality metrics.

Barrier: Restrictions on technology transfer caused by issues about intellectual property. Solution: Seek avenues of cooperation involving industry, academia, and government, including standardized protocols for transfer of technology for academic purposes (while encouraging industrial participation).

Barrier: The NIH review panels lack expertise to assess adequately the scientific merit and promise of new technologies. Solution: Form Special Emphasis Panels or invite outside reviewers as necessary when evaluating technology-based proposals.

Scientific Priorities

1. **Create and support an environment** in which bioengineering can play a leading role in interdisciplinary research and education.

2. **Establish databases of physico-chemical and physiological properties** of cellular and sub-cellular processes in human and model organisms with different genetic backgrounds and in different environments. Use these databases to formulate and analyze models that predict physiological function across hierarchical levels of the organism.

3. **Develop new technologies** to collect quantitative data ranging from the genome to the organism and to elucidate functional dynamics in living cells and tissues with sensitivity down to the level of single molecules.

Implementation Strategies

The NIH should identify the study of functional correlates of genomics as a major new initiative. One approach would be to establish Science and Technology Centers in academic institutions.

Imaging at the Molecular and Cellular Levels: Microscopic Foundations for Molecular and Cellular Engineering

Chairs: Mark H. Ellisman, Ph.D., and John G. White, Ph.D.

The biologist interested in understanding structure and function is constantly seeking new tools. Advanced capabilities for visualizing the structure and dynamics of individual molecules are being enhanced, and new methods for viewing and understanding how macromolecular and organelle-sized complexes operate can be expected as a consequence of current technological research.

Vision Statement

New developments in microscopies are providing crucial information and essential approaches for understanding the structure and function of cells and molecules. Molecular and cellular bioengineering is a rapidly evolving multidisciplinary area capitalizing on these technologies to create advances in research in many vital areas. The emergent microscopies are particularly critical in research on mechanical modeling of cells and tissues, interactions of implanted devices with host tissues, biosensors that monitor physiological processes, and prosthetics to augment deficient sensory systems.

Barriers and Solutions

Barrier: Major gaps exist in researchers' understanding of biological structures and their functions at the submicron level (1µm to 1nm). Solution: Recent developments in modern computer-aided light and electron microscopies and molecular probes offer great promise for delivery of vital new information. A partnership with the biomedical engineering community offers excellent opportunities for multidisciplinary development and application of carefully designed research tools that will better meet the requirements of the biomedical research community.

Barrier: Although X-ray and crystallographic techniques have provided high-resolution images of individual protein structures, understanding of how proteins form organized complexes and how these function within the living organism is lacking. Solution: New light microscopy techniques have enabled the dynamics of the internal machinery of living cells to be visualized at both structural and chemical levels. These techniques are currently being extended to cells within tissues or embryos. Similarly, the new electron microscopies can now yield atomic-resolution data from macromolecular structures or three-dimensional data at nanometer resolution from organelle-sized structures by electron tomography.

Barrier: The dramatic advances in identification of gene products from the genome projects require complementary technologies to realize the potential clinical benefits. Solution: Advanced microscopy techniques offer new diagnostic clues, such as specific chromosomal rearrangements that are indicative of certain types of cancer.

Remarkable developments have been made in the following techniques, but each is in a state of flux and has great potential for further development by multidisciplinary efforts:

- **Multiphoton microscopy** is benign to living tissue and permits deeper specimen penetration than other types of light microscopy.
- **Scanning probe microscopy**, such as atomic force microscopy (AFM), offers a potential bridge between light and ultrastructural microscopies, with possible application to living tissue.

- **Electron energy-loss spectroscopic imaging** provides elemental identification and clear images of relatively thick specimens and identification.
- **Transmission electron microscopes with field-emission guns** can provide near-atomic resolution for hydrated, frozen biological specimens when combined with three-dimensional reconstruction techniques.
- **Three-dimensional reconstruction from electron micrographs (tomographic and single particle averaging)** reveals structural details of large (>500 kDA) macromolecules, virus particles and organelle systems within cells as well as cell-cell attachments.
- **Fluorescent labels** are being used to measure intramolecular distances and to indicate domains of gene expression.
- **Physiological indicators** have been developed that indicate the physiological state of a cell, such as ion concentration or membrane potential.
- **Magnetic resonance imaging** is now being applied to the study of embryogenesis and is providing resolutions down to 10 nm.
- **Single-copy studies of proteins and oligonucleotides under physiological conditions** attain the ultimate limit of observation of an individual macromolecule.

Scientific Priorities

1. **Improve microscopes to fill the resolution gap.** There is a great opportunity for biologists and bioengineers to pioneer approaches for direct three-dimensional imaging in the size range between X-ray crystallography and traditional light microscopy. The large number of high-resolution structures already produced by X-ray crystallography far outstrips investigators' ability to assemble these structures into functional "machines." This mismatch will be made worse as high-resolution structural techniques are applied to the large number of unsolved protein structures. In addition, some aspects of structural biology currently lie beyond the reach of X-ray crystallography (e.g., membrane proteins and protein dynamics). The technological gap needs to be closed by building better tools, including three- and four-dimensional imaging, to advance our understanding of structure, function, and dynamics in this important spatial domain.
2. **Develop better probes.** Probes have become a vitally important component of all forms of microscopy. They provide information on molecular identity, intracellular environment, and intramolecular measurements. A more integrated approach to the development of probes is needed. Such an approach will require multidisciplinary initiatives involving chemists, biologists, molecular geneticists, bioengineers, instrumentation specialists, and laser physicists. There is particular promise in the development of engineered protein-based probes and probes that can be used for integrated microscopy—i.e., combinations of light and electron microscopy.

Implementation Strategies

Accomplishing the objectives arising from the opportunities stated above will require development of critical human resources. This can be achieved by funding multidisciplinary training grants that cut across the traditional boundaries of the physical and life sciences. These grants should be linked to technological research and development centers targeting the above objectives.

All of the challenges cited will be attacked best by a research-driven approach. The panel suggested fostering investigator-initiated approaches that address research challenges. A final suggestion was to develop interdisciplinary types of proposals that bring in scientists and engineers from outside the normal NIH catchment basin.

Imaging at the Tissue and Organ Levels

Chairs: Thomas F. Budinger, M.D., Ph.D., and Ruth E. Dayhoff, M.D.

Diagnostic imaging of tissues and organs, especially in the modalities of ultrasound, nuclear medicine, nuclear magnetic resonance and spectroscopy, and X-ray computed tomography, has been a field of rapid advances. Integration of the information content from the diverse imaging methods is required to reap the benefits of these advances. Emphasis must be continued on minimizing invasiveness, imaging and processing time, costs, and patient discomfort, as well as maximizing resolution and ease of use of data display. Bioengineering can play a crucial role in future improvements in each of the components of imaging research and development, from image acquisition to clinical decision-making.

Vision Statement

The methods of biomedical noninvasive and minimally invasive imaging can be placed into two major categories. Category I comprises methods in general use for diagnostic imaging of tissues and organs. Category II methods are those which have been introduced more recently and do not have wide applications to clinical studies, but do have promise for biomedical science investigations and diagnostics in animals and human subjects.

Category I

- X-ray projection imaging, including digital radiography and mammography.
- Ultrasound imaging, including Doppler flow and blood pool imaging.
- Magnetic resonance imaging (MRI), including magnetic resonance angiography and spectroscopy.
- Radionuclide imaging, including positron emission tomography (PET) and single photon emission tomography (SPECT).

Category II

- Electric source imaging (ESI), including magnetoencephalography, magnetocardiography, and surface potential mapping of brain potentials and thorax potentials.
- Optical imaging, including infrared tomography and fluorescent emission imaging (stimulated emission and photon emission from chemical reactions).
- Electrical impedance tomography.
- Endoscopy using multiple modalities including ultrasound, radiation sensors, and multispectral optical imaging.
- Electron spin resonance and microwave imaging – but both techiques have depth of penetration limitations that have prevented their application.

Research Strategies and Barriers

A systems engineering perspective of imaging technology research leads to a division of issues into three aspects, for which strategies of research and development promise to yield substantial improvements in our ability to detect, quantify, and understand biomedical processes by noninvasive imaging.

Strategies for making technology improvements include new approaches, such as exploring tissue characteristics by simultaneous use of ultrasound and MRI in which one mode stimulates a change that is detected by another mode. Such strategies also include improvement of well known methods, such as improved detectors for PET and new magnet configurations for MRI. The technological improvements possible for all of these methods include reduction of imaging and processing time, reduction of costs and patient

discomfort, visualization of tissue and organs in three-dimensions, and improvement in both signal-to-background contrast and spatial resolution .

But a separate and more comprehensive strategy of research is needed to enable human information integration. Under the category of systems engineering for human information integration is included research in visualization, modeling, simulation, and informatics (i.e., the timely delivery of organized information for clinical decision making). Research strategies are needed to optimize the acquisition, dissemination and interpretation of patient diagnostic information. This area of research will enable studies of efficacy and facilitate the necessary human engineering to obviate the scenario of a good new idea being developed into a discarded device through poor integration with the medical or research question.

A third class of strategies is needed to define the barriers which hinder biomedical imaging research and development. The following areas need scrutiny to discover barriers that can be safely removed to facilitate rapid deployment of new ideas and to integrate new methodologies in clinical and scientific medicine:

- Standards and regulations.
- Industry and government regulations. The representation by researchers on standards-setting bodies, including those of FDA, should be increased.
- Peer Review. A looser interpretation of hypothesis testing is needed to allow good fundamental physics and engineering projects to be favorably evaluated even without a close tie to a specific biological problem.

Scientific Priorities

1. **Improve imaging technologies** in the areas of spatial and temporal resolution, speed of information acquisition, detectors, and contrast resolution. Improvements in these areas by factors of 2–10 are physiologically possible, with even greater factors in the long term. Modalities beyond those in current medical practice have tremendous potential but definite technological barriers. The panel recommended an expansion of NIH support for instrumentation research.

2. **Develop improved contrast enhancement agents and probes** specific for molecular, cellular and physiological processes in both normal and disease states to promote medical science discoveries and development and verification of models and therapy. These probes include radiopharmaceuticals, MRI contrast agents, ultrasound contrast agents (general and receptor-specific), and methods of stimulating tissue response.

3. **Develop new and effective strategies for classification and estimation**, using synthesis and integration of multimodal imaging and modeling approaches with *a priori* information. An engineering systems approach for optimizing the integration of clinical image information for clinical decision-making, as well as research applications, is the underlying goal. A systems approach to deployment of medical imaging technologies in research applications is also needed.

Implementation Strategy

Whereas the first two recommendations can, in part, be satisfied by present NIH processes or those currently being developed, a new emphasis would be needed for the realization of the third recommendation. To that end, the panel recommended giving support to Centers of Excellence for Biomedical Imaging Research**,** which would include training. These Centers of Excellence would be responsible for the development, implementation and validation of strategies for assessment.

Instruments and Devices

Chairs: Linda M. Graham, M.D., and Erik L. Ritman, M.D., Ph.D.

Instruments and devices for both research and clinical use, from the exquisitely small nanoinstruments to whole organ and tissue replacements, have been developed by bioengineers. These instruments have significantly improved capabilities for research in animals, clinical diagnosis, and treatment of diseases and disabilities. Using principles of physics, chemistry, and biology, collaborative efforts of bioengineers, medical scientists, and clinicians will allow development and implementation of new instruments and devices that have improved accuracy, reliability, and biocompatibility. In addition, these devices may utilize concepts of "smartness," automaticity, and closed-loop control. As a result of novel instruments, clinicians and biomedical scientists will see new opportunities to discover basic physiologic and biochemical mechanisms and to intervene to correct pathophysiological conditions.

Vision Statement

The development of instruments and devices that augment or replace damaged organs or diseased tissues, thus restoring patients to health and independence, will occur by means of technological advances that combine principles of engineering, physics, mathematics, and chemistry with in-depth knowledge of biology. The NIH can facilitate achievement of this goal by supporting the multidisciplinary research necessary to develop the next-century instruments and devices.

Barriers

Although a revolution in molecular biology and gene therapy has occurred, the advances resulting from this revolution have yet to make the transition to the bedside. A variety of instruments and devices, ranging from delivery systems to sensors and imaging modalities, will be needed to apply gene therapy to clinical problems. Furthermore, the development of improved medical devices will require further advances in cellular and molecular biology.

A major obstacle to the optimal use of medical devices (especially implantable devices) is the continuing lack of biocompatible materials. The development of such materials and other enabling technologies is critical. The following is a partial list of required materials and technologies:

- Biocompatible materials,
- Power sources,
- Noninvasive monitoring and actuators,
- Implantable sensors,
- Instruments for the detection and control of disease processes such as infection, and
- Microdevices and microinstruments for use in small-animal models.

Other barriers that are impeding progress include the following:

- Lack of communication between the multiple disciplines involved in instrument and device development,

- Disparate needs and motivations of industry, research scientists, and regulatory agencies (for example, industry's financial backers generally expect the duration of development of a device to market to be no more than 3 years),
- Liability issues.

Solutions

- Targeted efforts to increase the knowledge base and its application to the development of biocompatible devices and instruments,
- Support for multidisciplinary workshops and conferences (modeled after the now-defunct NHLBI contractors meeting),
- Establishment of new mechanisms to encourage industry-academic collaborations (modeled on the NSF Engineering Research Centers program or other programs),
- A workshop focused on risk/benefit and liability issues.

Scientific Priorities

The NIH should embrace the development of technology to support health as part of its mission. The following are important goals in the area of instruments and devices:

1. **Understand the host-implant interface** to enable the development of biocompatible materials that resist infection, thromboembolism, uncontrolled inflammatory response, and fibrosis.

2. **Develop the capability to monitor device function**, identify early signs of failure, and implement corrective measures.

3. **Support a registry or database** that provides researchers, manufacturers, and consumers with access to information about device performance over time.

Implementation Strategy

The recommendations above should be implemented by enhancing mechanisms to foster collaborations among multiple disciplines as well as among industry, government, and academia. In addition to the usual research support mechanisms, consideration should be given to the following:

- Bioengineering technology centers modeled after NSF engineering centers,
- Fellowship/training programs on implantable device research,
- Program announcements, and
- Workshops.

Mathematical Modeling

Chairs: Van C. Mow, Ph.D., and H. Steven Wiley, Ph.D.

Mathematical modeling is an analytical tool for understanding complex data sets and biologic phenomena and is a source of quantitative hypotheses incorporating multiple interacting biological processes at various hierarchical scales. Mathematical modeling has a powerful predictive role, especially in areas that are not readily approached experimentally or ethically. Recent advances in understanding the physical properties of biologic materials and fundamental advances in the molecular basis of cell behavior have greatly expanded the research opportunities and usefulness of mathematical modeling.

Vision Statement

The success of reductionist and molecular approaches in modern medical science has led to an explosion of information, but progress in integrating information has lagged. There is a need to make connections among facts, but this is hampered by inherent biological complexities and problems of translating information between different experimental spaces, e.g., structural, spatial, and temporal. Mathematical models provide a rational approach for integrating this ocean of data, as well as providing deep insight into biological processes. The integrative capacity of models will be needed in translation efforts to bring knowledge gained from molecular studies to the physiological level needed for treatment of disease. Modeling should not be seen as an afterthought, but as a critical component of multidisciplinary projects. To foster such recognition, the scientific community needs improved communication between modelers and biological scientists and improved educational opportunities for those involved in multidisciplinary projects. Scientific leaders should raise the bar for what is expected from hypothesis-driven science. Mathematical modeling is a glue holding together various experimental and interpretive modalities.

Goals for the Next 5–10 Years

- Improve the infrastructure for modeling, increasing training grants, fellowships, and sabbaticals.
- Increase the number of engineers/modelers who have experience with biological systems.
- Implement disease-based models that can be experimentally tested.
- Create at least six centers that focus on collaborations between biologists, engineers, and bioengineers, with an emphasis on integrative modeling of biological and biomedical problems.

Barriers and Solutions

Barrier: Biologists and modelers often do not understand each other's language. This inhibits collaborations and mutual respect. Solution: Improve educational opportunities in terms of training grants, joint meetings, and fellowships.

Barrier: The perception that models must be in an advanced state of development to be acceptable for funding. Solution: Place more mathematically trained scientists on scientific review panels to provide an appropriate perspective.

Barrier: The perception that models are not relevant to biological problems. Solution: Couple modeling to experiments by tightly integrating experimental results with the evolution of models.

Barrier: Difficulty in obtaining appropriate data for modeling. Solution: Educate scientists on what is needed for modeling and implement Web-based database solutions to provide modelers access to appropriate data.

Barrier: Redundant modeling efforts. Solution: Maintain Web-based linkage between research groups involved in modeling.

Scientific Priorities

1. **Establish long-range multidisciplinary research centers** composed of biologists, biomedical scientists and bioengineers with emphasis on mathematical modeling—both mechanistic and phenomenologic approaches—to study critically important clinical problems, such as:
   - Drug delivery to hard-tissue tumors,
   - Biomechanical etiology of osteoarthritis,
   - Fluid dynamic factors in atherosclerosis, and
   - Infectious disease transmission modalities.

   Of particular interest is the exploration of phenomena that, for ethical or economic reasons, are not appropriate for direct experimental studies.

2. **Establish training fellowships** (including graduate research assistantships, postdoctoral fellows, sabbatical leaves for senior faculty and industrial researchers) for programs with emphasis on mathematical modeling to enhance collaboration in multidisciplinary studies.

Implementation Strategies

- Convene a workshop on mathematical modeling with broad coverage of various critically important basic science and clinical problems. Workshop participants should include biologists, biomedical scientists, and bioengineers who have pursued various aspects of mathematical modeling. The workshop should be required to produce a symposium volume on state-of-the-art mathematical modeling methodologies and problems that have effectively and explicitly benefited from the results of mathematical models.

- Create multidisciplinary modeling centers that focus on clinically important diseases and basic biological problems that will benefit from such focused research programs.

- Provide predoctoral and postdoctoral training grants and sabbatical programs for both senior academic and industrial researchers interested in mathematical modeling of critically important biological and clinical problems.

- Generate shared experimental resource centers to promote the development of mathematical and computer models for biomedical problems—employing biologists, biomedical scientists, and bioengineers with emphasis on mathematical modeling expertise.

Medical Informatics

Chairs: Paul D. Clayton, Ph.D., and Casimir Kulikowski, Ph.D.

Medical informatics is the study and evaluation of information structures (data and knowledge) and the methods by which information can be used to affect health care delivery, education, and research. Information can be used as a specific intervention in diagnoses and therapies in ways similar to the uses of procedures, devices, and pharmacological agents.

Vision Statement

Medical informatics and bioengineering have potentially symbiotic capabilities that require integration and recognition of complementary strengths. Both fields involve acquiring, processing, and analyzing information. They share the need to manage massive, distributed, networked data sets that are compiled from heterogeneous sources. These databases serve a heterogeneous set of users, with roles in research, patient care, and education.

Methodologies for addressing clinical issues and educational materials may be productively applied to biological and genomic information. Medical records are required to assess the capabilities of medical devices and to design bioengineering experiments. Information obtained by sensors and imaging and assay methods can contribute to the detail and richness of the data set for a patient. As researchers advance the ability to describe a person's genomic profile, genomic and medical records databases converge. This convergence will improve care by increasing understanding of diseases that might develop and responses to specific therapies and by answering questions about patient populations.

Trends

Electronic medical records systems are emerging as a solution to the problem of managing patients across a variety of caregivers and under severe economic pressures. Hospitals and managed care organizations are, for the first time, investing in these systems to influence caregivers at the point of care, to gather information about expenditures, and to analyze effectiveness of expenditures.

Collaborators are developing standards for vocabularies, messaging, and formats to collect, collate, and share data. However, financial support is needed to allow them to devote the time required to deliver the standards in a mature form.

Home- and community-based access to health records, monitoring and intervention, and communication and education are increasing rapidly. Now that four or five notable prototype systems have been observed for a number of years, a broad-based commitment to installing such systems across the spectrum of health-care delivery sites is emerging. Vendors are beginning to present products that are acceptable for use.

Goals for the Next 5–10 Years

- Develop and apply classification systems and standard terminology to improve health care and reduce costs. Such standards will improve the utility of clinical databases for clinical research purposes and facilitate exchange of clinical data for both care and research.
- Develop techniques to incorporate imaging and voice data in electronic patient records. Such information must be classified and stored in a manner that permits the extraction of data for analysis.
- Develop nomenclature and methods of discerning information from whole body images of patients, when it becomes possible for such images to be stored as part of

the medical record. It may be desirable to correlate physical features of such images with genetic information.
- Develop tools for managing and filtering large quantities of data, such as information residing on multiple Web sites and the map of a person's genetic makeup.
- Create better techniques to facilitate the accurate and efficient collection of information from physicians, other health professionals, and patients. Methods may include user-friendly remote sensing devices for home and community use.
- Develop methodologies to support the transfer and application of population-based health information in clinical settings.

Barriers

The inability to collect patient data and knowledge is an immense, unsolved problem that inhibits appropriate intervention. Other barriers include:
- Lack of standards; and
- Lack of methodology for selecting, aggregating, integrating, summarizing, verifying, validating, and managing the content of large databases.

Solutions

- Understanding the impact on the delivery of health care of Next Generation Internet capabilities and functionality.
- Voice and gesture recognition, multimodal interfaces, mobile/nomadic computing, metadata, ontology development, visual indexing, and processing of information.
- Authentication methodology.
- Database mining and data models.
- Standards for vocabulary, message formats, and domain- and task-specific interchange formats.

Scientific Priorities

1. **Develop methods for structuring, managing, and analyzing large, distributed, networked, adaptive databases**: multimedia medical records, genomics, directories, World Wide Web literature, clinical trials, registries, rules, pathways, knowledge structuring, data mining, etc.
2. **Develop methods for acquiring patient data and knowledge**: natural language processing, nomadic/mobile computing, gesture recognition, image/multimedia compression, interfaces.
3. **Develop methods for delivery of reusable knowledge at the point of service**: online records, vocabulary, indexing.
4. **Develop methods for sharing knowledge for multiple purposes** and updating disseminated information as it is superseded by more recent data.

Implementation Strategies

- The NIH and the health care community must participate actively in the development of specifications and standards for the Next Generation Internet.
- Standards and techniques to protect confidentiality of patient data must be improved. Such standards and techniques must adhere to the “four A’s”—authentication, access privileges, audit trails, and accountability.

Nanobiotechnology

Chairs: Harold G. Craighead, Ph.D., and Kensall D. Wise, Ph.D.

Challenges and opportunities exist for the design, fabrication and use of nanometer scale structures as probes of the structural and functional properties of biological macromolecules, as biosensors, and as central components of diagnostic and therapeutic approaches.

Vision Statement

Nanobiotechnology will generate new capabilities, facilities, and approaches for investigating and understanding cellular and molecular processes. These advances would not be possible using macroscopic technologies. Nanobiotechnology will allow for a dramatic miniaturization and integration of complex functionality for a new class of biomedical devices and microsystems and will lead to development of improved device-tissue interfaces to permit their long-term use *in vivo*.

Goals for the Next 5–10 Years

The next decade will be a period of increasing research in nanobiotechnology and can be expected to yield important results. Great attention will be paid to issues relating to surface interactions, which become critical as dimensions decrease and surfaces dominate devices. The diverse and complex interactions between biological systems and inorganic material surfaces will be one focus for investigation and development and may lead to important breakthroughs in the biocompatibility of a variety of implantable monitoring and therapeutic devices.

A new understanding of biological systems may emerge through, for example, the ability to analyze in detail many individual cells rather than average properties. Rapid analysis of the genetic material from a single cell or chemicals expressed by a single cell could enable new modes of disease diagnosis and improved understanding of complex physiology. Future devices and biomedical instruments will involve increasing levels of integration, analogous to the development of integrated electronic circuits but with the need to deal with significantly more diverse material and structural systems. The integration of fluidics, optics, mechanics, and electronics at the micro- and nano-scales will enable increasingly complex functions and systems to be miniaturized and mass-produced. Current development of DNA analysis chips is the first example of such integration.

Barriers and Solutions

The diversity of material systems and their limited compatibility with biological systems present substantial challenges in nanofabrication. There is a lack of understanding of biological and physical phenomena at nanometer-scale dimensions. The design, fabrication, and integration of ultra-small, complex systems will require advanced, complex fabrication technologies and significant technological development. This will require understanding and expertise from many diverse disciplines and associated experimental methods. The disciplinary barriers that often exist in established organizations must be bridged.

The challenges are substantial, yet the potential for important intellectual and technological payoffs underscores the need for solutions to the barriers and challenges. The following actions are suggested:

- Encourage the assembling of required experts to attack the research problems. There are a number of good examples within the NIH of multidisciplinary, goal-oriented programs.
- Support research and development of the underlying technologies.
- Recognize the fundamental importance of surface studies, fabrication technology, process integration, and materials development to the successful development of nanobiotechnology, and leverage new initiatives targeting specific biological problems with existing and emerging efforts supported by engineering and physical sciences, e.g., within NSF and the Department of Defense.

Scientific Priorities

1. **Develop nanostructures and technologies for the selection, manipulation, and analysis of single cells.**

2. **Develop nanostructures and technologies for the selection, manipulation, and analysis of individual molecules.**

3. **Develop engineering nanostructures, integration strategies, and surface technologies to support needed mechanical, optical, chemical, and electrical interactions with biological systems**.

Implementation Strategies

- Encourage novel and high-risk research approaches and support appropriate interdisciplinary group approaches to advance nanobiotechnology.

- Take advantage of and leverage ongoing/emerging activities in areas – such as micromechanics, microfluidics, integrated optics, novel materials, tissue engineering and patterning techniques – that can provide paths by which device and material developments can be addressed.

New Approaches to Therapeutics

Chairs: Gail K. Naughton, Ph.D., and Andrew S. Wechsler, M.D.

Development of new modes of therapy is hampered by the lack of understanding of the pathogenesis of disease, the lack of predictive animal, in vitro *and cellular models for the study of disease mechanisms, the lack of adequate delivery systems, and the inability to noninvasively monitor delivered drug or cell therapy* in vivo *for assessing efficacy of the therapy.*

Vision Statement

In the future, the field of therapeutics should advance drug delivery, tissue engineering, and genetic engineering by integrating the expertise of cell biologists, bioengineers, and medical scientists to develop tools to better assess the physiological barriers to entry of therapeutic agents, the directed delivery of those agents, and the persistence of the physiological effect.

Goals

- Create and maintain more robust animal models of human disease.
- Create a biological transport map to predict where the infused products will go.
- Develop physiologically based mathematical models to better predict delivery and *in vivo* remodeling and integration.
- Develop better imaging techniques to trace delivery.
- Develop noninvasive methods for *in vivo* sensing of biologic consequences of therapies.
- Develop better understanding of cell and tissue structure change during normal embryogenesis and disease states to better target desired action.
- Develop methods to enhance cell and tissue specificity of therapeutic interventions.
- Develop chemical-containing polymers that direct cell and tissue differentiation and integration and that are ultimately replaced by tissue.
- Develop cell control systems (presumably gene or regulatory-region based) that regulate cell differentiation. These systems should be applicable to stem cells, allogenic tissue, and xenogenic tissue.
- Develop a database of tissue and use properties that influence the transport of therapeutic agents (e.g., cell pore sizes, interstitial organization, diffusion characteristics, and vascular permeabilities).
- Develop molecular fingerprinting that will allow investigators to match the therapeutic agent to the molecular makeup of the specific tumor.
- Develop better understanding of stem cells, progenitor cells, and cell differentiation and de-differentiation.

Barriers and Solutions

Barrier: Inadequate understanding of physiological barriers to delivery (intravascular, transvascular, interstitial, and cellular barriers). Solution: Create bioengineering centers for delivery of therapeutics.

Barrier: Absence of effective animal models for specific diseases. Solution: Make this a scientific priority.

Barrier: Poor understanding of cell differentiation, proliferation, signaling of cells to initiate tissue development, and integration of various cell types into functional three-dimensional structures. Solution: Make this a scientific priority.

Barrier: Inadequate collaboration among cell biologists, bioengineers, and physicians. Solution: Create new interdisciplinary courses of instruction and conferences, and prioritize interdisciplinary grant applications.

Barrier: Lack of adequate imaging systems for monitoring *in vivo* delivery, persistence, and function of new therapeutics. Solution: Provide education and training grants, and make this a scientific priority.

Barrier: Paucity of standards for biological constructs to assess important parameters of cell activity, matrix ratios, and biomechanical characteristics. Solution: Develop and establish consensus standards in collaboration with ASTM and ISO.

Scientific Priorities

1. **Create substitute tissue and synthetic organ constructs** by combining the sciences of tissue engineering and genetic therapy.

2. **Develop delivery systems for therapeutic agents** that are target-specific, that address transport barriers, and that access the targeted areas in optimal quantities and remain in the area for predictable and adequate lengths of time.

3. **Develop *in vivo* systems that can be interrogated** to provide efficacy of new therapeutic agents.

Implementation Strategies

- Stimulate the submission of proposals targeting both businesses and universities for interdisciplinary programs in the field of new therapeutics.

- Sponsor and encourage the development of Bioengineering Centers (both physical and virtual) for the most costly of the goals defined above and provide easy access as information evolves.

- Create a therapeutic Web site accommodating the various interests of individual scientists.

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