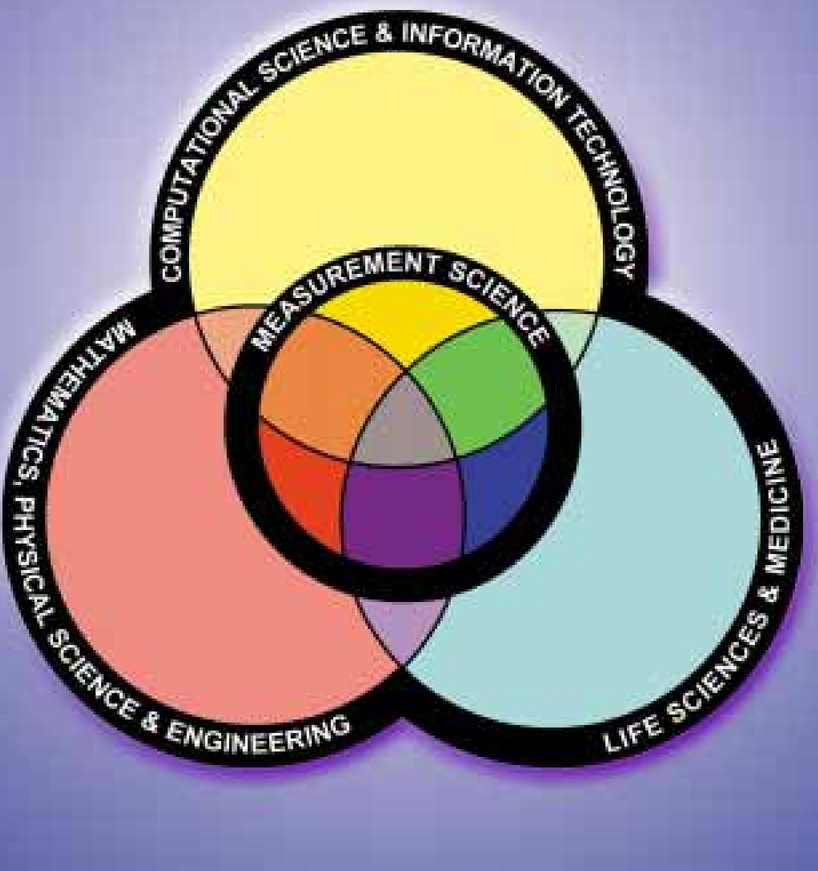
Analytical Instrumentation

for the

Next Millennium



Report of a Workshop and Symposium

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Additional Information

Website Location: *http://www.emsl.pnl.gov:2080/docs/ainm*

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Executive Summary

Today the United States leads the world in economic vitality and quality of life. However, sustaining this position is contingent upon our continued leadership in science and engineering and in developing new technologies. Recent advances have brought us to the threshold of achieving a molecular-level understanding of the underlying scientific issues related to several critical technologies—notably, creating advanced materials with novel properties, establishing the genetic basis of disease in plants and animals, and understanding human impact on our natural environment. Reaching this understanding early in the 21st century means unprecedented further advancements in the molecular sciences and the likewise progression of the measurement sciences—the generator of tools and skills needed to enable these advancements.

Developing measurement tools of unmatched specificity and sensitivity is central to the requisite molecular-level understanding of complex systems—to define molecular interactions and their time evolution. Moreover, the challenge of solving increasingly complex problems, with the accompanying paradigm shift from hypothesis-driven to information-driven science, places a premium on rapid, parallel, and inexpensive measurements. These trends are especially evident in the Human Genome Project, in combinatorial chemistry, and in the study of the chemical networks that control cell function.

As we move from the "century of physical sciences" to the "century of biology" and confront the formidable technical challenges inherent in trying to understand complex systems, we are experiencing a dramatic change in the way science is practiced. Until recently, we relied entirely on theory and experiment to find answers to scientific questions. With the explosion of computer capacity and computational science, we have, for the first time, the capability to simulate and model systems considered too complicated to characterize experimentally with previously available technology. Moreover, management of information has become an essential component of modern science. Thus, mathematical modeling and simulation and information management have become two important new tools used to further our understanding of complex phenomena. The third essential tool is new instrumentation, which can provide experimental validation and correction to concepts and models and promote the creation of new ones. The synergistic application of these three tools to complex scientific problems can significantly advance technological progress in the 21st century.

The workshop on Analytical Instrumentation for the Next Millennium was organized to address the advancement of measurement science. At this workshop, which was held in Orlando, Florida, from March 5-7, 1999, leading measurement scientists from universities, national laboratories, and instrument manufacturers surveyed present capabilities and assessed future needs. The workshop participants concluded that present measurement capabilities and institutional structures are inadequate to respond to the technical challenges.

In this report we identify new approaches for advancing the capabilities of measurement tools in concert with the development of computational and modeling tools. The multidisciplinary integration of mathematical and physical sciences with engineering, life sciences, and informatics will redefine the measurement sciences. Advanced analytical instruments and new ways of practicing science will be created by multi-interdisciplinary teams composed of scientists from academia, national laboratories, and the private sector.

We identified five priority objectives for an expanded program in the measurement sciences that supports future developments, fosters a synergistic approach, and calls for a heightened level of education and training:

- Develop new instrumentation that falls into two broad categories
  - High-performance instruments of unprecedented precision, sensitivity, spatial resolution, or specificity.
  - Low-cost, robust instruments for monitoring and analyzing extremely small volumes, for remote operation, and for process control.
- Develop high-throughput instrumentation.
- Develop the techniques of informatics and mathematics needed to deal with very large data sets and very rapid data acquisition.
- Promote a synergy between instrument development and the fundamental understanding achieved through measurement to ensure that these two elements of progress reinforce each other.
- Integrate measurement science into the fundamental intellectual core of graduate education and training for scientists and engineers.

To achieve these objectives, we recommend a multi-agency, multidisciplinary initiative in measurement science be established and funded at $250 million, or 0.1% of the total annual U.S. research and development expenditures, which for 1999, was approximately $247 billion [NSF Report 99-357]. The proposed scale of effort is needed to achieve the advances in measurement capabilities essential for sustaining the Nation's multi-billion dollar research investment in molecular science.

"The effect of a concept-driven revolution is to explain old things in new ways. The effect of a tool-driven revolution is to discover new things that have to be explained."

— Freeman Dyson, *Imagined Worlds*
Harvard University Press (1997)

Introduction

The need for massively parallel, high-throughput, miniaturized, and widely distributed instrumental analyses, preferably with "smart" instruments that are self-calibrating and highly automated, is a response to the discernible shift at the close of the 20th century from hypothesis-driven to information-driven science and technology. Furthermore, there is a corresponding need for massive automation in data reduction, storage, retrieval, and graphic presentation. In the 21st century the interaction of theory, modeling, and simulation with measurement science will play a central role in the acquisition of information and its conversion into knowledge. New fundamental knowledge is essential to advance the measurement sciences, particularly in the drive to nano-scale science and technology. Increasingly precise and quantitative measurements are equally essential to advancing the acquisition of fundamental knowledge.

Advances in measurement science are uniquely important to advancing the molecular sciences on a very broad front—in the chemical and materials sciences, molecular physics and biology, nanotechnology, environmental science, electronics, and process monitoring. The basic principles of molecular structure and the properties of isolated molecules and bulk materials are now well established. However, the interactions of molecules, the role of inter- and intra-molecular forces in creating microstructures, and the dynamics of these interactions are only poorly understood. **Completing the task of defining the detailed relationships between molecular interactions, including the time dependence of the interactions responsible for self-assembly, and relating the extended network of molecular interactions to bulk properties of matter are grand scientific challenges for the 21st century.**

A workshop on Analytical Instrumentation for the Next Millennium (AINM) was held in Orlando, Florida, March 5-7, 1999. The Steering Committee, formed July 1998, included both instrumentation specialists and representatives of the major users of advanced instrumentation. The committee considered present challenges and opportunities in measurement science and anticipated needs for the next decade as a basis for developing an agenda, selecting speakers, and inviting participants. The invited participants represented academia, the instrumentation industry, and the government sector.

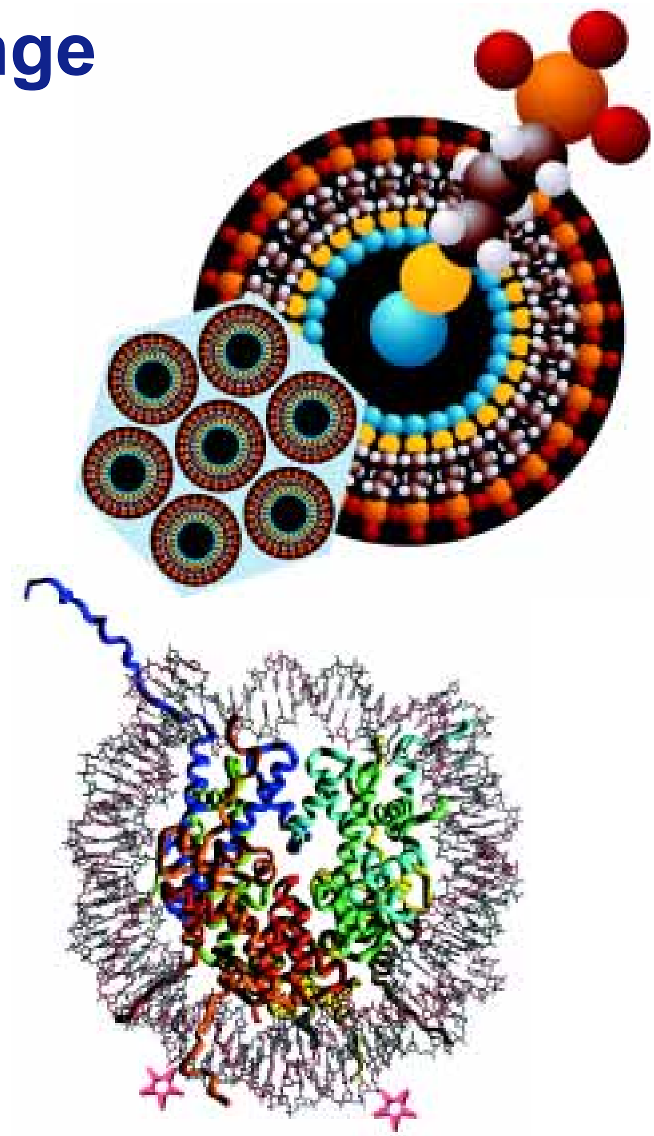
The workshop preceded the 50th Anniversary Meeting of the Pittsburgh Conference on Analytical Chemistry (Pittcon) in March 1999 so that the organizers could present a summary of their conclusions to instrument development leaders attending the conference. **An important objective of the workshop was to clarify the central role of measurement science in establishing a molecular-level understanding of matter.**

The remarkable progress made during the past decade—extending measurement sensitivity to the limit of single-molecule detection, dramatic miniaturization in devices adapted for nano-scale and micro-scale applications, and the imperative to incorporate mathematics and informatics into measurements—formed the basis for our discussions. **This report identifies new approaches for advancing the capabilities of measurement tools in parallel with the development of computational and modeling tools. The nature of the challenges that lie ahead is exemplified in the section entitled The Biological Imperative by discussing proteomics, the elucidation of protein structure and function.**

The logo designed for our report attempts to capture the themes and basic philosophy of the workshop. The design emphasizes the interconnected and interdisciplinary roles of fundamental science and applications as represented by the mathematical, physical, materials, and life sciences, and engineering, medicine, and informatics. The logo also reflects the unique role of measurement science in linking and enabling synergistic progress in these disciplines.

Additional workshop information is provided in the appendices: Appendix A lists AINM workshop participants; Appendix B lists the program for the AINM Workshop; and Appendix C lists the program for the Pittcon Symposium on Analytical Instrumentation for the Next Millennium. This Symposium was the first presentation to the scientific community of the deliberations and findings of the Workshop. Summaries of keynote presentations at the Workshop, plus summary reports from Breakout Discussion Groups, were subsequently placed on the Internet for review and comments. The Steering Committee prepared this report as the end product of our deliberations, with significant feedback from the scientific community.

The Central Challenge



As we move into the next century, molecular science faces major scientific challenges in the understanding and control of complex systems exemplified by the self-assembled monolayers on mesoporous supports material and DNA-protein complex pictured here.

As we move into the next century, the major scientific challenge of molecular science is to achieve understanding and control of complex systems. This challenge appears in different forms in materials science, in environmental science, and in biology. The central challenge from the perspective of materials science and engineering is to achieve an understanding of the continuum from the properties of individual molecules through nano-materials to the bulk properties of matter. In environmental science, the challenge is to understand the interrelations of chemical transformations, earth cycles, and biological processes. From the viewpoint of biology, the challenge is to understand how information in the genome is transformed into functional biology and how errors in the genome relate to disease. **It follows that the central challenge to measurement science is to provide the tools and methodologies for answering these complex, but intimately related, questions.**

Analytical instruments are tools for obtaining experimental information at the level of detail required to validate models and theories. Radical changes in instrument capabilities are required to respond to radically changing demands of the molecular sciences for new and different kinds of information. Dramatic expansion in computing power over the last few years has made theory, modeling, and simulation of molecular phenomena equal partners with experimental approaches for obtaining new knowledge. Further expansion in computing power will place the routine modeling and simulation of very complex problems within our reach early in the 21st century. **Parallel advances in instrumentation will provide essential validation of models and allow information to be converted into fundamental knowledge.** Analysis of data in real time and integration of information from databases into the interpretation of measurements will add another dimension to measurement science.

Additional challenges include development of massively parallel, fully automated analytical instruments, and of "smart" instruments that are self-calibrating and self-correcting. These instruments will multiplex several analytical methods. They must meet the requirements for characterization of the products of combinatorial chemical synthesis, correlation of molecular structure with dynamic processes, high-resolution definition of three-dimensional structures and the dynamics of their formation, and remote detection and telemetry.

Also needed are capabilities for structural and dynamics measurements on micro- and nano-scales for the characterization of molecular assemblies. Reduction in size to the micro-scale and nano-scale levels generates demands for greatly increased instrument sensitivity and for new mathematical approaches to pattern recognition and graphics display. The dramatic increase in the surface-to-volume ratio as sample size is reduced requires new fundamental knowledge of interfacial and transport phenomena. New technologies that permit multiplexed measurement at higher spatial resolution and greater molecular specificity are emerging, and established technologies are being further developed to enhance speed, resolution, and sensitivity. Finally, the impending revolution in rates of data generation presents formidable challenges for storage, analysis, and correlation of data.

Three unifying themes emerged in our discussion of these topics and challenges:

1. As materials science moves to micro-scale and nano-scale dimensions, the demands of this field for higher resolution and specificity are merging with analogous demands from environmental science and from molecular biology. In particular, as the focus shifts from micro-machining technology to self-assembly mechanisms driven by molecular forces, solutions to materials problems become biomimetic in nature. Similarly, characterization of environmental samples will require molecular information on a nano-scale to investigate past or present biological activity.

2. Mechanistic understanding of nano-scale phenomena in the material, environmental, and life sciences requires measurement in the time domain of the dynamic properties of individual molecules and of assemblies of molecules. Significant advances in measurement science are required to characterize the evolution in time of molecular structure and composition. This level of detail is essential to understanding molecular self-assembly in living and non-living systems.

3. The systems approaches of the engineering sciences emerge as promising approaches to understanding functional biology, environmental systems, and properties of materials. Multidisciplinary teaming, which combines the physical, mathematical, computational, and life sciences with engineering, will become the only practical approach to solving these complex problems. To meet these challenges, the analogous multidisciplinary teaming approach is required in the measurement sciences.

> ***"In almost every branch of science, and especially in biology and astronomy, there has been a preponderance of tool-driven revolutions. [The discipline of] physics has had great success in creating new tools that have started revolutions in biology and astronomy."***
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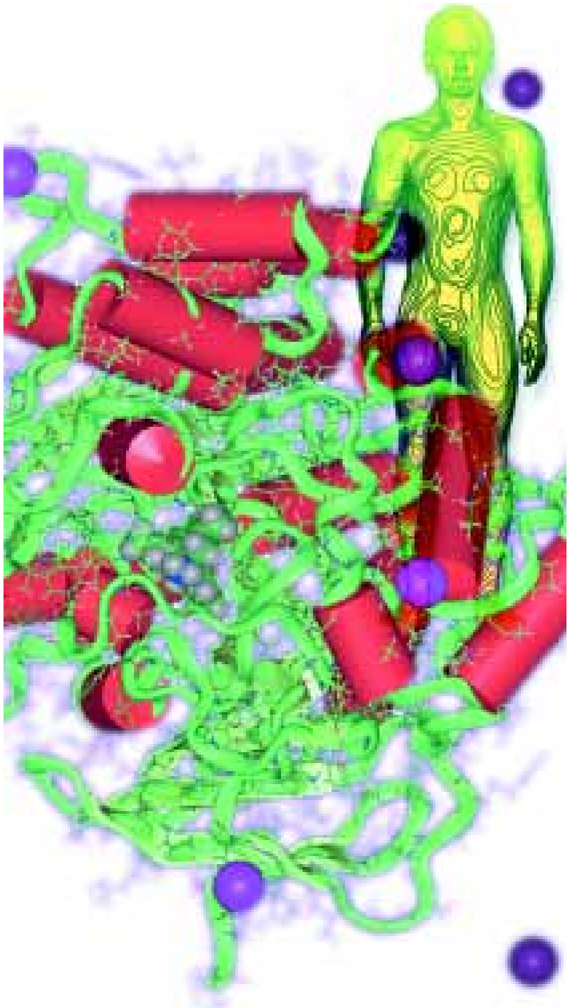
> Freeman Dyson, *Imagined Worlds*
> Harvard University Press (1997)

The Biological Imperative

From the realm of materials, environmental, and biological sciences, we focus here on proteomics to provide a more detailed example of the need for revolutionary improvements in measurement.

The recent, spectacular progress in the Genome Project, including new analytical strategies for sequencing DNA and the vast volumes of information already produced and catalogued, has catalyzed astonishing discoveries in functional biology and molecular medicine. This success, in turn, has prompted us to use a similar framework for describing the measurement challenges that are involved in taking the life sciences to the next level of molecular understanding of biology. The advances that must be made include spatially resolving and tracking in real time the chemistry within living cells; this should include the chemistry at the interface between synthetic materials and biomolecules within living organisms. The goal is to achieve a molecular-level, predictive understanding of interactions within and between cells that will lead to understanding at the level of the organism. The Genome Project endeavors to decipher the chemical code fundamental to all organisms, including humans, other animals, microbes, and plants. It has catalyzed changes both in our understanding of biology and in our approaches to science. Before the Genome Project, hypothesis-driven science dominated biology, just as it has dominated the physical sciences. The Genome Project introduced a new approach—namely, discovery-driven science—in which the focus is to identify all the elements of a particular system without reference to hypothesis.



Understanding the chemistry of the living cell presents a grand scientific challenge that posits extraordinary opportunities and challenges for measurement science as we enter the 21st century.

The synergistic intersection of hypothesis-driven and discovery-driven approaches has revolutionized contemporary biology and will revolutionize the practice of medicine and agriculture in the 21st century.

Reflections on the Genome Project a decade from now are likely to focus on four striking contributions. The first is the generation of what can be called the periodic table of life. This includes the identification of control regions for gene expression, structural motifs in genes and proteins, and the characterization of the molecular basis for polymorphism (variation within a species), including variations in appearance, physiology, and disposition to disease. The second contribution is the comparative analysis of complete genome sequences. The ability to determine the strategies of information handling in living organisms and to compare strategies across divergent species will revolutionize our understanding of life. The third contribution is the creation of global measurement technologies that generate quantitative data with high throughput and high reproducibility. These technologies already have changed how we do certain types of biology. Finally, the fourth contribution of the Genome Project is the catalysis of a series of paradigm changes in biology that are transforming the practice of the life sciences, with profound implications for the production of food and the treatment of disease.

The sequencing of entire genomes will be recorded as a truly remarkable and transforming achievement of 20th century science and technology. The next challenge is to interpret this genetic information and thereby enable the transformation of fundamental and applied biology from descriptive to predictive sciences. Defining the molecular interactions that convert the information stored in our genes into this machinery of life is dramatically more difficult than establishing the molecular sequences that constitute the instruction set. Accordingly, understanding the chemistry of the living cell presents a grand scientific challenge that posits extraordinary opportunities and challenges for measurement science as we enter the 21st century. The relevant scientific questions in post-genomic biology—as defined for us by the extraordinary achievements of the Genome Project—are summarized by:

- **How is the information stored in the genome translated into the myriad of interconnected informational pathways that constitute the living cell?**
- **How are signals from the environment integrated into the responses of living cells?**

Increasingly, biological studies at the molecular level will be directed towards the study of living systems rather than isolated components. Accordingly, biological systems must be studied by analyzing the behaviors of all of their elements taken together. This systems analysis logically would proceed in four phases: (1) define the elements of the system and their interconnections; (2) perturb the system, and measure quantitatively and dynamically how the system changes; (3) build mathematical and statistical models that predict systems behavior; and (4) compare predicted and actual responses until a satisfactory system model has been constructed. Sensitive, quantitative measurement tools that can acquire, display, and interpret biological information in living cells and organisms with high throughput are essential to enable this new era of systems biology.

Elucidating the molecular processes that occur in an individual cell will require the development of powerful new analytical measurement tools capable of unprecedented spatial resolution. Microelectrodes that electrochemically detect specific DNA molecules already have been reported in the literature. The next challenge is to develop arrays of ultra-small, rapidly responding sensors for quantitatively measuring multiple components (i.e., proteins, signaling compounds, and others) in complex systems and tracking changes in their concentration with time.

Currently, genomics employs several different types of commercially available measuring devices for sequencing, mapping, and detecting amplified DNA. Many of these tools—such as capillary gel electrophoresis, DNA hybridization arrays, and mass spectrometry—originated in research laboratories that focused on chemical measurement science. New analytical tools are now under development for more detailed examination of DNA, such as robust detection of single nucleotide polymorphisms (SNP), and for detection and structural characterization of covalent DNA modifications. These next-generation tools will enable studying both variations in genetic information and the impact of those variations on the organism. In turn, new tools that enable temporal and spatial resolution of changes in living (and therefore, dynamic) systems will follow. These tools might include molecule-specific ultra-microelectrodes and specifically-interacting, fluorescent, reporter molecules. The combination of several measurement techniques for simultaneous measurement in real time will provide especially powerful methods for studying molecular interactions.

The lynchpin in the study of complex systems biology is proteomics, which is the global study of proteins. Proteins play central roles in connecting genes to functions in an organism. It is critical to recognize that proteomics presents much more difficult challenges to measurement science than did genomics. There is no technique for replicating proteins to increase the amount available for analysis; this contrasts sharply with DNA, for which the polymerase chain reaction (PCR) is used to synthesize copies of the DNA fragment to be analyzed. Consequently, orders-of-magnitude improvement in detection of individual proteins is needed. Because each protein has a unique structure, experimental determination of protein structure plays an essential role in proteomics. Unlike the structure of DNA, the structure of a protein cannot yet be predicted from knowledge of primary sequence. However, this structure defines how a protein interacts with other molecules in a complex system. Thus, the determination of the three-dimensional structure of proteins is an essential additional task for proteomics, one that was not required to determine the sequence of a genome. Moreover, a myriad of post-translational chemical modifications—for example, phosphorylation, glycosylation, and methylation—present dozens of variations of a single protein that can affect its function.

Even greater challenges include the characterization of protein interactions, identification of proteins in complex biological assemblies (e.g., transcription complexes), and the delineation of protein function in informational pathways. To meet these formidable challenges, particularly at the cellular level, new analytical tools must be created with greater information content, higher sensitivity, enhanced detection limits, higher throughput, and lower cost. **Creating these new tools will require both breakthroughs in current technologies and invention of totally new concepts in analytical measurement.**

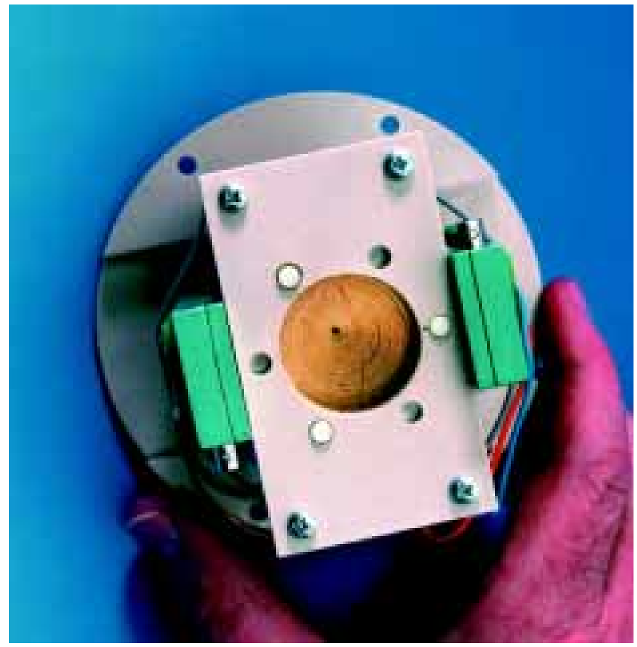
X-ray crystallographic techniques are a mainstay for the determination of protein structure. X-ray instruments, especially those based on synchrotron radiation, must be highly automated as we enter the post-Genomic era. New approaches for automating the production of protein crystals for X-ray studies are needed, including purification and crystallization steps. Powerful laboratory X-ray sources based on laser technology may open many opportunities for protein crystallography and X-ray scattering studies.

A next-generation of specialized neutron facilities enabling small angle neutron scattering (SANS) will reveal details of the interactions in protein complexes. Development of enhanced computational methods to model SANS data is critically needed to support this powerful structural technique. As more powerful neutron sources are developed (such as the Spallation Neutron Source currently under construction), the ability to obtain data on biological samples using SANS, neutron diffraction, neutron reflectometry, and other methods will be significantly enhanced. Because biological samples require both high flux and a low noise background, new beamline facilities and instruments specially designed for biological studies will be needed.

Further developments in biological mass spectrometry will also be critical to advances in proteomics. Mass spectrometry shows great promise for studying protein complexes. It is also uniquely suited for identifying minor modifications in a protein that can affect reactivity in a biological system. Mass spectrometry is inherently one of the most sensitive and versatile tools for structural studies. The extension of mass spectrometric capabilities to higher mass, greater resolution, higher sensitivity, and greater dynamic ranges is required to provide the quantitative data (amounts of proteins as well as their identity) required for proteomics. In addition, a critical need exists for developing highly efficient methods for introducing sub-picomole samples into the mass spectrometer. New means of manipulating trapped ions may allow complex mixtures and effluents from single cells to be introduced and analyzed without prior chromatographic separations.

Nuclear magnetic resonance (NMR) spectroscopy and other spectroscopies are evolving essential tools for characterizing the dynamics of living organisms and for analyzing the dynamic structure of proteins. Recent exciting developments in imaging of single cells with NMR spectroscopy provide high spatial resolution combined with chemical composition and the time evolution of molecular structures. Continued developments in high-field NMR spectroscopy and highly sensitive microprobes, along with multiplexing of NMR spectrometers, optical microscopes, and multi-photon spectroscopies, will provide insights into the structure and function of supramolecular assemblies and cellular components. The combination of NMR spectrometers with other spectroscopies as imaging tools will play an increasingly important role in the study of complex systems.

We expect that many other "conventional" analytical techniques will evolve dramatically to meet the challenges in the study of complex systems. Perhaps the most notable example is the recent development of micro-fluidic devices in which conventional chemical reactions, sample handling, separation steps, and detection have been engineered to fit on a single chip. Although these technologies are not yet applied routinely in a biological laboratory, combining multiple analytical steps in a single device to enhance sensitivity, reduce sample losses, and improve throughput is truly revolutionary. As these devices are developed, they will require new approaches for detection, including new lasers and optical devices. Bringing the microelectronic industry's expertise to bear on the needs in analytical instrumentation in the next millennium is of extraordinary importance.



Revolutionary devices are needed to improve sensitivity of analytical devices. This recently developed "ion funnel" enhances mass spectrometry sensitivity for electrosprayed ions by two orders of magnitude.

The development of advanced electrochemical methods will enable the creation of temporally and spatially resolved chemical maps within cells. When integrated on a single chip with electrochemical sensing, electronic circuits can resolve signals faster and more sensitively than conventional circuits employed in current analytical instruments. Multi-parameter, high-speed cell sorting and micro-imaging techniques are essential for studying processes at the cellular level. Marking specific molecules on cell surfaces or within cells (e.g., with fluorescent tags or redox centers) will increase throughput and sensitivity. Combinatorial chemistry presents unique opportunities for generating molecules to serve as specific tags. High-throughput, multi-parameter assays are essential to define the consequences of genetic, biological, and chemical perturbations on entire biological systems. These represent only a few of the types of technologies that must be developed for elucidating and monitoring information pathways in living cells and organisms.

Computer science and applied mathematics are critically important partners in measurement. They are indispensable in obtaining both qualitative and quantitative information and then storing, manipulating, analyzing, displaying, and finally integrating the information into models. These branches of science will play an essential intellectual role in the post-Genomic era. Modern computational methods will play crucial roles in proteomics and in systems biology. With anticipated advances in computer hardware and software, bioinformatics and mathematics will increasingly determine how measurement science is applied to biological systems. New computational methods must be developed to predict the biologically relevant three-dimensional structure of a folded protein from its primary amino acid sequence. Similarly, computational methods will help predict the function of a protein from its three-dimensional structure using techniques such as automated comparisons of predicted structures against libraries of three-dimensional functional motifs. Moreover, high-speed networking is indispensable for connecting collaborating scientists at dispersed locations and for enabling display, sharing, and integration of information and research protocols.

Continued developments in high-field NMR spectroscopy and highly sensitive microprobes will provide insights into the structure and function of supramolecular assemblies and cellular components.

Education and Training

Measurement science is conceptualized in this document as an emerging cross-disciplinary intellectual endeavor that is related to, but significantly broader than, the sub-disciplines of analytical chemistry, biosensing, or molecular physics. Realizing the potential of measurement science will require a motivated and highly trained workforce and mandates significant change in graduate and postgraduate education. None of the challenges we have discussed can be addressed effectively without a strong emphasis on cross-disciplinary development of technology through the teaming and partnership of scientists and engineers. It is important to realize that language barriers between different scientific and engineering disciplines are significant. Biologists, chemists, computer scientists, electrical engineers, chemical engineers, mechanical engineers, physicists, and mathematicians must learn the languages of other fields in order to communicate.

Training graduate students and postdoctoral fellows with two or more mentors from different disciplines is an important and possibly essential strategy for training leaders of the future in these cross-disciplinary efforts. Cross-disciplinary training of mature and young scientists is essential for unveiling the molecular, life-sustaining processes of the living cell, understanding molecular transformations in the environment, and predicting the performance of materials from molecular structure. The requirements for knowledge-based and interpersonal skills are so diverse that postdoctoral fellows will be important in the development of the measurement tools described in this report. Until graduate education evolves to meet the need of multidisciplinary teams that focus on instrumentation development, the skills acquired through traditional Ph.D. programs must be augmented. The most important element is the multidisciplinary, problem-solving environment that must be fostered if we are to make rapid progress in solving these complex problems.

Members of research groups engaged in the development and deployment of novel instrumentation must master the fabrication of devices using principles of chemistry, electronics, optics, materials science, and engineering. With increasing emphasis on miniaturization and parallelization, nanotechnology will become more important. Instrument development also requires computer hardware and software to provide the interface among measurement devices, computers, human operators, and databases. In addition, we believe that development of new instrumentation must be motivated by significant analytical problems in disciplinary research. Consequently, in addition to understanding modern measurement science and technology, a successful student apprentice in the measurement sciences must learn the language and concepts of the target area of disciplinary research. Mastery in this second area is not required, but the subject must be appreciated sufficiently to discuss the measurement objectives with experts. Without this communication, the student may not appreciate the required sensitivity and precision and likely sources of errors originating in the system being analyzed. Furthermore, the student must develop enough understanding of engineering to help engineers translate measurement objectives into engineering specifications for an instrument.

Mastering this ability to communicate with practitioners in multiple disciplines is required. Measurement science requires too much knowledge in too many fields for one individual or even a small group of similarly trained individuals to succeed. Communication skills and the ability to work in teams are critical for success. Fortunately, these skills also provide a foundation for success in all areas of the scientific workforce, whether in national laboratories, research institutes, universities, or the private sector.

Infrastructure

We share the belief that the traditional departmental structures of universities discourage multidisciplinary research and training, especially in cases that mix elements of basic and applied research. Many universities have developed non-departmental units in which multidisciplinary research and training are encouraged. Federal granting agencies can foster this evolution in education by providing long-term, programmatic support of instrument development. Some of this additional support could be in the form of awards to individual investigators. However, the most effective, directed funding mechanism to stimulate instrument development will be awards to groups of faculty committed to the multidisciplinary approaches needed to address complex problems. The obvious benefit to students (and to their future employers) is broader knowledge and skill. More subtle, but equally important, is mutual respect among groups of scientists and engineers with different interests, aptitudes, and backgrounds.

Two types of multidisciplinary groups or centers emphasizing measurement science were discussed at the workshop. The most common center is oriented toward particular types of instrumentation or specific applications. The National High Magnetic Field Laboratory, a cooperative effort among units of the University of Florida, Florida State University, and Los Alamos National Laboratory, is an example of an instrumentation-oriented center, whereas the Microfabrication Center at Cornell University is an example of an application-oriented center. These centers are staffed by scientists and engineers who are experts in particular kinds of instrumentation or in particular applications. Their senior staff members are among the leaders in the technique or field that defines the center.

Because such centers are typically very costly to establish, they are justified only in a few areas of recognized importance. The second kind of instrumentation center focuses on the conception, design, construction, and evaluation of novel instrumentation, rather than on specific instruments or specific applications. Such a center must have all the skill sets required to create the next generation of instruments, for example, expertise in robotics, computation, and informatics. This kind of center will be capable of addressing a variety of problems, and its focus is expected to change as scientific problems are solved and other frontier fields emerge. Elements of such centers can now be found within several universities and Federal laboratories. However, no such center

The National High Magnetic Field Laboratory, an NSF-sponsored cooperative effort among units of the University of Florida, Florida State University, and Los Alamos National Laboratory, is an example of an instrumentation-oriented center.

currently exists with a full complement of needed skills and a broadly based focus on instrumentation development and measurement science.

An instrumentation center of this kind requires a professional staff with expertise in a broad range of topics such as optics, electronics, computers, signal processing, transduction, chemistry, biology, physics, and informatics. It also requires a defined "user community" that is interested in taking advantage of its capabilities. The center should build upon existing collaborations and strengths and should involve partnerships among universities, industrial firms, and government laboratories. Such a center would require space not only for permanent staff members but also for users who visit the facility and participate in the development of instrumentation for specific purposes. Funding arrangements should be flexible and should include seed money for short-term collaborations and pilot projects designed to explore the feasibility of instrumentation development on a larger scale.

The consortium is another concept for a multidisciplinary center that can be greatly enhanced by recent developments in information technology and that may be especially valuable in accessing the wide range of skills required for instrumentation development on the scale we consider necessary. New distributed computing and communications technologies are being deployed to enable researchers to access data, instruments, and expertise regardless of their location. These advanced computing and communication technologies create opportunities to revolutionize not only the scope but also the process of scientific investigation. We examined a number of examples of scientific user facilities and institutes that have demonstrated successful remote operation of sophisticated instruments, maintenance of shared notebooks, video conferencing, and development of research publications involving wide geographic distribution of the collaborating scientists. Effective teaching and learning of instrumental methods and remote access to powerful research instruments, primarily by undergraduate institutions, have also been demonstrated. At the U.S. Department of Energy's William R. Wiley Environmental Molecular Sciences Laboratory, a Virtual NMR Laboratory is now fully operational. About half of the external users of this national scientific user facility now are accessing the laboratory remotely.

The completion of the Information Superhighway and advances in computing speed, power, and data storage capabilities can, in principle, largely remove geographic limits to effective collaborations of multidisciplinary teams. The inclusion of virtual multidisciplinary centers for measurement science will facilitate collaborations on a national and, eventually, a global scale. We therefore suggest that a subset of the Information Technology for the 21st Century Initiative be focused on the development of virtual laboratories with emphasis on broad access to high-performance instruments.

Technology Transfer

The AINM workshop briefly considered barriers to technology transfer that might be encountered by developers of novel instrumentation concepts in academic, industrial, and national laboratory environments.

The transition from concept to commercial product may be viewed as proceeding from conceptualization to proof-of-principle, then to functional prototype, and finally to a robust engineered product capable of being marketed, used, and maintained. The cost associated with instrument development increases substantially with each step in this sequence. Entrepreneurial inventors, academic institutions, and instrument manufacturers often disagree as to what constitutes a proof-of-principle model or a functional prototype. One-of-a-kind research tools rarely meet criteria of instrument manufacturers for functional prototypes, and extensive research and development may be required to transform a laboratory-scale model to an acceptable prototype. Along with conflicting views of the value of intellectual property, these issues frequently are impediments to technology transfer, especially when concepts and working models originate in academic laboratories. It is our consensus that many good ideas are lost to the scientific community (and to industrial research and technology) at the intersection where effective research tools are converted to functional prototypes.

The broadly based instrumentation centers described earlier appear to be the best model for addressing these problems. First, the broad technical expertise available at multidisciplinary centers is critical to converting the "effective research tool" prototype typically created in a university laboratory to the more professional "functional prototype" desired by industry. This reduces both the uncertainties regarding instrument performance and capabilities and the cost to create a robust prototype that can be manufactured. Secondly, partnering scientists and engineers from academia, national laboratories, and the private sector in such a center has the potential to bring these communities together to promote a common understanding of the complex process of innovation in creating high-technology measurement systems.

The broader scope of issues—involving economic conditions, patents, management of intellectual property, and so on—that hinder or facilitate the transfer of technology from scientific laboratories to commercial practice was recognized by the workshop, but considered beyond its purview.

Response to the Challenge

As we move from the "century of the physical sciences" to the "century of biology" and confront the formidable technical challenges to understanding complex systems, we are experiencing a dramatic change in the way science is practiced. Until recently, we relied on theory and experiment alone—which clearly implies measurement of all the important variables—to find answers to scientific questions. The power of modern computers gives us for the first time the capability to simulate and model systems considered too complicated to characterize experimentally with present technology. Moreover, management of information has become a key component of modern science. Mathematical simulation and modeling and informatics are now important new tools used to develop understanding of complex phenomena. The third essential tool needed for developing molecular-level understanding of complex processes remains new instrumentation that can provide experimental validation and correction to existing concepts and models and promote the creation of new ones. The synergistic application of these three tools to complex scientific problems can significantly advance technological progress in the 21st century.

> ***Enabled by convergence of information technolgy and measurement sciences, the intersection of hypothesis-driven science with information-driven science in the next millennium will lead to breakthroughs in knowledge and understanding.***

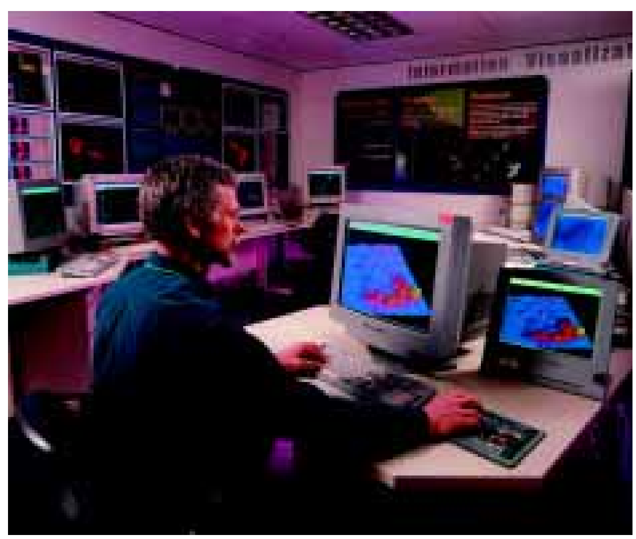
Developing new measurement tools of unprecedented specificity and sensitivity is central to achieving a molecular-scale understanding of complex systems—to define molecular interactions and their time evolution. Moreover, the challenge of solving increasingly complex problems and the accompanying paradigm shift from hypothesis-driven to knowledge-driven science places a premium on rapid, parallel, and inexpensive measurements. These trends are especially evident in deciphering the human genome, in designing materials tailored to specific functions, in understanding the molecular processes controlling the characteristics and functions of living cells, and in understanding the complex interactions of chemical, biological, and geological processes in the environment.

Specific new approaches should be considered to advance instrumentation in parallel with the advancement of mathematical modeling and informatics. Centralized funding provides the mechanism for multidisciplinary integration of mathematical and physical sciences with engineering, biology, and informatics required for transforming advances in measurement science. Explicitly, we recommend that the pressing needs described in this report be addressed by establishing at least five centers, with appropriate geographical distribution, for instrumentation research and development. In conjunction with this initiative, individual or small group awards to academic investigators, which cost less and therefore can afford more risk, can be used to explore unproven concepts, unknown techniques, and revolutionary ideas. (Supplements could be provided to successful projects to encourage collaboration with instrument manufacturers and with innovative emerging companies.) Of the five nationally distributed centers, at least two should be multipurpose instrumentation centers. The remaining centers might appropriately be focused on a technique (e.g., NMR spectrometry, mass spectrometry, electrochemistry, X-ray lasers) or on an instrumentation-limited problem area (for example, proteomics, cell signaling, or nano-materials).

Measurement science in general could be advanced by interfacing high-data-acquisition rate instruments to moderate-to-high-performance computers with informatics capabilities and real-time graphic displays. High-speed data links to massive data bases and establishment of virtual laboratories are needed to foster remote linkage of scientific specialists to specialized information and tools. These areas of emphasis should be included within the framework of the Information Technology for the 21st Century, which underscores the critical importance to the United States of maintaining leadership in information technology in order to sustain its economic prosperity.

Within the framework of individual investigator awards, the funds available for instrumentation research should be increased by at least 50 percent. Supplemental funding of existing awards to encourage collaborative research with center specialists should be considered. The IGERT program of NSF is ideally suited to play a strong role in instrument development and as a focus for the training of students.

Accomplishing these goals at the scale needed to ensure success will require a multi-agency, multidisciplinary measurement science initiative funded at approximately $250 million annually. Sustaining this level of investment over a five-year time frame will permit an assessment of its impact on developments in nanotechnology, systems biology, national security, and human health. We think it probable that an even greater investment may be justified by such an analysis. **This recommended investment of 0.1% of total U.S. annual research and development expenditures is appropriate to achieve advances in measurement capabilities that are essential to sustain the Nation's multi-billion dollar research effort in the molecular sciences.**



Computational simulation and modeling are important tools for understanding complex phenomena. Equally important is new instrumentation that can provide experimental validation and correction to concepts and models and promote the creation of new ones.

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Appendix B

Workshop Agenda

Friday, March 5, 1999

Time	Speakers	Presentation Topics
8:30-8:45 am	Jean Futrell	Introduction to Workshop and Charge to Participants
8:45 – 9:15 am	Michael Hunkapiller	Bio-Assay Challenges in Molecular Medicine
9:15 - 9:45 am	Robert Austin	Single Molecule Spectroscopy
9:45 - 10:15 am	Jonathan Sweedler	Microseparations Combined with Information-Rich Detection
10:15 – 10:30 am		Break
10:30 – 11:15 am	David Rothman	Data Management in a Distributed Analytical Environment
11:15 - 12:00 pm	Ray Bair	Virtual Laboratories: Distributed, Collaborative Research Environments
12:00 - 1:45 pm	Working Lunch	Breakout Sessions (Session Leaders)
		"High Throughput Analyses" (Michelle Buchanan, Bonner Denton)
		"Interaction of Radiation with Matter" (Lance Taylor, Sandy Asher)
		"Characterization of Interfacial Phenomena" (Steve Bernasek, Jeanne Pemberton)
		"Process Control and Monitoring" (Mike Angel, Mel Koch)
1:45 - 2:15 pm	Alan Marshall	Ultra High Performance Mass Spectrometry
2:15 - 2:45 pm	Ron Coifman	The Mathematics of Complex Images
2:45 - 3:15 pm	Gerard Morou	Ultra High Performance Lasers
3:15 - 3:30 pm		Break
3:30 - 5:30 pm	Breakout Sessions (Leaders)	"Infrastructure / Interdisciplinary Centers" (Gary Hieftje, Art Janata)
		"Micro- and Nano-Structures" (William Smith Rees, David Rakestraw)
		"Translation of Concept into Practice" (Sally Swedberg, Drew Evans)
		"Informatics" (Robert Austin, Skip Garner)
8:30 pm	Tony Czarnik	Cubes and Tubes, Tips and Chips: Methods for Combinational Discovery

Saturday, March 6, 1999		
Time	**Speaker, Discussion Leaders**	**Presentation Topic/Discussion**
8:30 – 9:15 am	Lee Hood	Genomics and Proteomics: High Throughput Analytic Tools
9:15 - 12:00 pm	Breakout Session Reports and Feedback Session	
9:00 - 9:20 am	Michelle Buchanan, Bonner Denton	"High Throughput Analyses"
9:20 - 9:40 am	Lance Taylor, Sandy Asher	"Interaction of Radiation with Matter"
9:40 - 10:00 am	Fred Hawkridge, Adam Heller	"Characterization of Interfacial Phenomena"
10:00 - 10:20 am	Mike Angel, Mel Koch	"Process Control and Monitoring"
10:20 - 10:40 am	Break	
10:40 - 11:00 am	Gary Hieftje, Jeanne Pemberton	"Infrastructure / Interdisciplinary Centers"
11:00 - 11:20 am	William Rees Smith, David Rakestraw	"Micro- and Nano-Structures"
11:20 - 11:40 am	Sally Swedberg, Drew Evans	"Translation of Concept into Practice"
11:40 - 12:00 pm	Stan Williams, Skip Garner	"Informatics"
12:00 - 2:00 pm	Jean Futrell	Lunch Break, Jean Futrell meets with Breakout Session Chairs to Develop Consensus Bullets; Steering Committee sub-group to plan Grand Challenge / Intellectual Content Breakout Sessions
2:00 - 3:00 pm	Sandy Asher	Grand Analytical Challenges for the Next Millennium
3:00 - 4:00 pm	Gerald Selzer	Intellectual Content of Interdisciplinary Instrumentation Research
4:00 pm	Jean Futrell	Summary of Workshop: Tentative Conclusions, Themes, and Recommendations

Appendix C

Pittcon '99 Symposium

Analytical Instrumentation for the Next Millennium - arranged by
Jean H. Futrell of University of Delaware

Monday Afternoon, Room 206A

Jean H. Futrell, Presiding

University of Delaware

Introductory Remarks—Jean H. Futrell

1:35 (176) **Introduction to the Symposium and Synopsis of a Workshop**— JEAN H. FUTRELL, Chair, Willis F. Harrington Professor of Chemistry, University of Delaware

2:10 (177) **Genomics and Proteomics: High Throughput Analytic Tools**— LEROY HOOD, Gates Professor and Chair Molecular Biotechnology, University of Washington

2:45 (178) **Challenges for Biological Assay Systems in the Coming Era of Molecular Medicine**— MICHAEL HUNKAPILLER, President Perkin-Elmer Biosystems and Vice President of Perkin-Elmer Corporation, Perkin-Elmer Company

3:20 **RECESS**

3:35 (179) **Ultrahigh-Performance Mass Spectrometry in the Next Decade**— ALAN MARSHALL, Director, Ion Cyclotron Resonance Program, National High Magnetic Field Laboratory and Professor of Chemistry, Florida State University

4:10 (180) **Assaying Neurotransmitters with Microseparations Combined with Information Rich Detection**— JONATHAN SWEEDLER, Professor of Chemistry and Engineering/Bioengineering, Beckman Institute - University of Illinois

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Staff in the University Printing Office, University of Delaware, assisted in the layout and printing of the report.

Nothing begets good science
as much as the development
of a good instrument.

Sir Humphrey Davy (1778-1829)