

# **BEYOND THE MOLECULAR FRONTIER**

## **CHALLENGES FOR CHEMISTRY AND CHEMICAL ENGINEERING**

Committee on Challenges for the Chemical Sciences in the 21st Century

Board on Chemical Sciences and Technology  
NATIONAL RESEARCH COUNCIL  
*OF THE NATIONAL ACADEMIES*

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<sup>2</sup>Committee membership ended March 2002, following Meyer's retirement from DuPont.

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# Preface

At the start of this project, the Committee solicited input from the chemical sciences community. The request for input was sent via e-mail to a large number of scientists and engineers, and a general request for information appeared in *Chemical & Engineering News*.<sup>1</sup> The committee received many valuable ideas in response to these requests. Additional input from the broader community was obtained as the committee wrote this report, when individual members of the committee consulted with their colleagues to obtain specific and detailed technical input. The committee is pleased to acknowledge all these contributors; a listing of their names and affiliations is presented in Appendix C.

This study was conducted under the auspices of the National Research Council's Board on Chemical Sciences and Technology with assistance provided by its staff. The committee also acknowledges this support.

Ronald Breslow and Matthew V. Tirrell  
Co-Chairs  
Committee on Challenges for the Chemical  
Sciences in the 21st Century

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<sup>1</sup>"Your Ideas, Please!" Madeleine Jacobs, Editor-in-Chief, *Chemical & Engineering News*, 78(14), April 3, 2000.



## Acknowledgment of Reviewers

This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the NRC's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

Richard C. Alkire, University of Illinois, Urbana-Champaign  
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Paul S. Weiss, The Pennsylvania State University

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations nor did they see the final draft of the report before its release. The review of this report was overseen by Pierre C. Hohenberg, Yale University, and R. Stephen Berry, University of Chicago. Appointed by the National Research Council, they were responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

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*Who of us would not be glad to lift the veil behind which the future lies hidden; to cast a glance at the next advances of our science and at the secrets of its development during future centuries?*

*David Hilbert, 1900, Paris*



# Executive Summary

This report continues the tradition of the last half-century—carrying out a periodic examination of the status of the chemical sciences. Where are we, how did we arrive at the current state, and where are we headed? These studies have been conducted, at the request of federal agencies, by committees of the National Research Council and its Board on Chemical Sciences and Technology (BCST). The reports that result from these efforts can be used by students and other researchers, agency officials, and policy makers in setting their own agendas and advancing the case for the field. The earlier reviews in the chemical sciences were *Chemistry: Opportunities and Needs*<sup>1</sup> (the Westheimer report), *Opportunities in Chemistry*<sup>2</sup> (the Pimentel report), and *Frontiers in Chemical Engineering: Research Needs and Opportunities*<sup>3</sup> (the Amundson report).

This report, which constitutes the overview for the committee's study of Challenges for the Chemical Sciences in the 21st Century, departs from the earlier practice of treating chemistry and chemical engineering as separate disciplines. Here, research, discovery, and invention across the entire spectrum of activities in the chemical sciences—from fundamental, molecular-level chemistry to large-scale chemical processing technology—are brought together. This reflects the way the field has evolved, the synergy and strong couplings in our

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<sup>1</sup>*Chemistry: Opportunities and Needs*, National Research Council, National Academy Press, Washington, D.C., 1965.

<sup>2</sup>*Opportunities in Chemistry*, National Research Council, National Academy Press, Washington, D.C., 1985.

<sup>3</sup>*Frontiers in Chemical Engineering: Research Needs and Opportunities*, National Research Council, National Academy Press, Washington, D.C., 1988.

universities between research and education in chemistry and chemical engineering, and the way chemists and chemical engineers work together in industry. The committee uses the term *chemical sciences*, or occasionally *chemical sciences and engineering*, to represent the field in which chemists and chemical engineers work. The disciplinary structures of chemistry and chemical engineering are discussed in Chapter 2 to explore their implications for future developments. We conclude that science has become increasingly interdisciplinary, and it is critical that the disciplinary structures within our fields not hinder the future growth of chemical sciences into new areas. Interdisciplinary refers here both to the strong integration from the molecular level to the process technology level *within* the chemical sciences and to the intersections of the chemical sciences with all the natural sciences, agriculture, environmental science, and medicine, as well as with materials science, physics, information technology, and many other fields of engineering.

Chapters 3 to 11 of the report then take up particular areas of fundamental or applied chemistry and chemical engineering. Each chapter starts with a specific list of some important challenges for the future. Then the chapter has a section on goals of the field, a section on progress to date to meet those goals, a section on challenges and opportunities for the future, and finally a section on why this is important.

Chapter 3 examines synthesis and manufacturing, with an emphasis on the unique aspect of the chemical sciences. A key goal of the chemical sciences is the creation of molecules and materials that do not exist in nature. Just as astronomers endeavor to investigate and understand the inner secrets of the stars, chemists and chemical engineers seek to unravel the fundamental principles that govern the properties and reactions of atoms and molecules. But in the chemical sciences it is also common to extend the goal beyond what *does* exist to the synthesis and study of what *could* exist, and to the manufacturing of new chemical products. Synthetic chemistry combines both aspects. The combined efforts of chemists and chemical engineers can be used to invent new ways to make molecules and new ways to manufacture them—whether these molecules provide new substances or just a new source of known substances. The ability to design and synthesize new substances offers the possibility of improvement on what is found in nature—with both accomplishments and future opportunities that range from lifesaving drugs to materials that can help to make our lives safer and more pleasant. We conclude that synthesis and process engineering play a central role in our field. Synthesis is the key to creating the substances we study and work with; larger scale chemical processing is the only way most chemical technologies can be developed and realized.

Chapter 4 discusses chemical and physical transformations of matter, both those that occur naturally in the environment and in living organisms and those that are invented by chemical scientists. The study of transformations spans the range from efforts to gain a fundamental understanding of naturally occurring

catalysts such as enzymes to the design of new catalysts for industrial processes. A century ago, chemists had only begun to interpret chemical transformations in terms of atoms, molecules, and chemical bonds—and now they are seeking ways to observe the details of reaction for an individual molecule. Dramatic changes have taken place in the chemical and physical processing of materials, where product properties and flow characteristics can be understood on the basis of intermolecular forces. This fundamental understanding can be used to design manufacturing methods with unprecedented reliability. In both synthesis and manufacturing, biochemical methods are increasingly important.

The time scales for which measurements are made also have undergone a phenomenal evolution. A hundred years ago, it was difficult to measure events taking place at a time scale of less than a second, and by the middle of the 20th century, the limit had changed by only a few orders of magnitude. But as described in Chapter 4, advances in the chemical sciences have moved the frontier to the investigation of processes that take place on the femtosecond ( $10^{-15}$  s) time scale—the time scale at which individual chemical bonds are made and broken. We conclude that the opportunities for detailed understanding of chemical reaction pathways and of the mechanisms of physical transformations represent an exciting challenge for the future that will add to the fundamental science of our field and to its ability to manipulate reactions and processes for practical applications.

The broad topic of analysis is treated in Chapter 5, which covers isolating, identifying, imaging, and measuring chemical substances and determining their molecular structures. The changes in capability and methodology are astounding. A century ago, Jacobus van't Hoff and Emil Fischer received the first two Nobel prizes in chemistry, respectively, for proposing the theory of tetrahedral carbon and for synthesizing all eight stereoisomers of glucose to corroborate that theory. These “simple” determinations of chemical structure required years of work. By the mid-20th century, spectroscopic techniques had made it possible to investigate far more complicated structures, and to detect them at much lower levels. But measurements at the parts per million level were still a challenge, and structure determination was no easy task—even when nuclear magnetic resonance became available in the 1960s. Chemical instrumentation has changed the frontiers for measurement in astonishing ways since then. The speed of measurements has been reduced from hours to small fractions of a second, and measurements can be repeated quickly to provide high throughput for multiple samples. The control of chemical processes in real time is drastically improved with new measurement techniques. Routine analysis can be done on samples in the range of milligrams to micrograms rather than on samples of a gram or more. The size of molecules that can be analyzed in detail has grown from organic molecules with molecular weights of several hundred daltons to proteins and nucleic acid polymers that are millions of times larger. And the sensitivity of modern instruments has moved the frontiers of detection from the level of one mole toward that of a

single molecule, an astonishing change of more than 20 orders of magnitude. We conclude that the area of analysis and structure determination presents important and exciting needs and opportunities, challenges such as detecting toxic or explosive materials in the environment, detecting land mines, and making chemical manufacturing processes more efficient and environmentally friendly via real time control.

Chapter 6 deals with computation and theory, from the most fundamental aspects to the role that this subject plays in manufacturing. The computer revolution has made it possible to approach a number of important goals: predicting the properties of unknown substances, predicting the pathways of chemical and physical processes, and designing optimal processes for manufacturing useful substances. However, these goals have not yet been fully achieved. When they have been, and the challenges in this field are met, we can expect to be able to create and manufacture new substances that have drastically shortened development times, thus bypassing substantial amounts of empirical experimental work and optimally meeting our needs in areas such as medicine and advanced materials. We conclude that this area of research has tremendous promise and importance, and that the opportunities should be pursued vigorously.

Chapter 7 describes the interface of chemistry with biology and medicine, ranging from the basic understanding of the molecular processes of biology, through the contributions of chemistry in modern agriculture, to the important role that medicinal chemistry plays in our health. Much, indeed most, of the progress in modern biology has relied on discovering the chemistry that underlies biological phenomena. Among the myriad examples are discovery of the molecular structure of DNA and sequencing the human genome. However, we still face enormous tasks in our efforts to fully understand the chemistry of biological processes. Modern medicinal chemists have invented, and chemical engineers have learned how to manufacture, the medicines that have let us conquer many diseases, but there is still much to do. New technologies such as microarrays for gene sorting are driving biochemical sciences, while others such as engineering of tissue regeneration are arising from advances at the biochemical frontier. We conclude that this area is extremely important in both the opportunities for fundamental discovery and the challenges and opportunities for curing human diseases.

Chapter 8 deals with the design and manufacture of materials, an area in which chemistry and chemical engineering play the central role; there is considerable overlap with the field of materials science, which is built on chemistry, chemical engineering, electrical engineering, and physics. We are familiar with such advances as modern plastics, paints, fabrics, and electronic materials, but great opportunities and challenges for the future still remain. As one example, materials with useful superconducting properties will have a huge impact on our lives if they can be developed in a way that permits practical transmission of large electrical currents over long distances without resistive loss. We conclude that the opportunities for the invention and production of novel materials with excit-

ing new properties make this one of the areas of greatest opportunity for future research and development.

Chapter 9 addresses atmospheric and environmental chemistry, where there are both fundamental and practical challenges. In the fundamental area, chemists, chemical engineers, and other environmental scientists need to explore the detailed chemistry that occurs on our planet—in the atmosphere, the oceans, the lakes and rivers, and in the earth itself. This is part of the general drive to understand the world we live in. However, there are great practical consequences as well. We need to learn how we can live in a world with an increasing population that needs and desires many of the products of modern technology, while we at the same time ensure that we do not damage the environment. The goal is a system that is fully sustainable—that will safely provide the energy, chemicals, materials, and manufactured products needed by society while neither irreversibly depleting the earth's scarce raw materials nor contaminating the earth with unhealthy by-products. We conclude that the basic understanding that will result from meeting the challenges in this area is absolutely critical for the future of the inhabitants of the earth, human and otherwise.

Chapter 10 deals with energy, including alternative sources and possible approaches to solving problems that have serious environmental consequences. In our quest for suitable sources of energy, appropriate ways to transfer it, and efficient ways to use it, we need to develop an approach that is sustainable and will not exhaust our resources or pollute our environment. We conclude that the practical challenges in dealing with energy needs are enormously important, and that we will need significant new developments in basic science in order to meet those challenges.

Chapter 11 addresses national and personal security, both the role that the chemical sciences can play in dealing with terrorist threats and the other ways in which national and personal security depend on current and future advances. There are serious challenges in this area. How can we detect chemical or biological attacks? How can we deal with them when they are detected? How can we provide improved materials and weapons to our armed forces, and to our civilian police? What can we contribute to increase the security of the average citizen? We conclude that this is an area where the chemical sciences are particularly central and relevant.

The final chapter of this report, Chapter 12, provides our view of some of the steps that might be taken to enhance the effectiveness of chemistry and chemical engineering in contributing to human welfare and understanding. We conclude that chemists and chemical engineers need to be prepared to work increasingly in multidisciplinary teams, and that this will change the way we educate future chemical scientists. We conclude that chemists and chemical engineers must put much more effort into effective communication with the media, and with students from kindergarten up. We also urge that our profession make much more effort to attract women and minorities.

We urge that educators revise undergraduate and high school courses in chemistry to make them broadly appealing to students with a variety of interests, and that teachers in grades K-12 invite chemical scientists to speak with their students about the challenges and opportunities waiting for those who choose to become scientists. We also urge that students get into research as soon as possible, so they can learn what it is that scientists find so exciting.

We urge that we cooperate with the media in explaining the achievements and goals of the chemical sciences, and that the general public encourage their sons and daughters to consider careers in science to help solve the challenges we have identified. We urge government agencies and private foundations to support the fundamental research that underlies applied science, in addition to supporting the applied science itself. We urge that chemically based industry also support university research and education, and continue progress in Green Chemistry, with its important environmental benefits.

We conclude that the chemical sciences and engineering have not only a great past but an even more exciting future, but that we will need to communicate more effectively with our fellow citizens, and will need their support so that we can indeed make the contributions that we see as possible.

The project on Challenges for the Chemical Sciences in the 21st Century will produce a series of reports in addition to this overview. These reports, each written by an independent committee and using input obtained at a corresponding workshop, also avoid the traditional disciplinary constraints of chemistry and chemical engineering. Instead, each workshop is organized around a specific area of societal need—materials and manufacturing, energy and transportation, national security and homeland defense, health and medicine, computing and communications, and environment. These topics were also discussed in the earlier BCST report, *Critical Technologies: The Role of Chemistry and Chemical Engineering*.<sup>4</sup> Each report addresses the same set of questions in relation to the particular area of its focus:

- *Discovery*: what were the major discoveries and advances in the chemical sciences during the last several decades?
- *Interfaces*: what were the major discoveries—and what are the challenges—at the interfaces between the chemical sciences and such areas as biology, environmental science, electronics, medicine, and physics?
- *Challenges*: what grand challenges exist in the chemical sciences today, and how will advances at the interfaces create new challenges in the core disciplines?
- *Infrastructure*: what changes in structure and support will be required to permit future advances in the chemical sciences?

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<sup>4</sup>*Critical Technologies: The Role of Chemistry and Chemical Engineering*, National Research Council, National Academy Press, Washington, D.C., 1992.

We believe our report and its sequels will be of value to those who want to know—and critically evaluate—the status and future goals of the many important sectors of the chemical sciences. What are they aiming to do, and how close are they to some of the goals? How should the chemical sciences be measured, as a field, against some of these goals? The chemical sciences must remain ambitious if the United States is to maintain its scientific and technological leadership, and if we are to make the maximum possible contribution to human welfare. The field will need to maintain its health and vigor if it is to attract an appropriate share of the very best minds. It will be necessary for chemists and chemical engineers to produce major new discoveries, revolutionary new technologies, and important new additions to the quality of life for our society. The chemical sciences and engineering must also stand ready to play a major role in assisting our nation and shaping its policies to benefit all of our population, and indeed all of the world.

The report closes with our vision of Some Grand Challenges for the Chemical Sciences. These are intended not to constrain the activity of research but to challenge the creativity of practicing scientists and engineers, to stimulate young people to join them in meeting these challenges, and to engender the enthusiasm of decision makers that is needed to support continued efforts of chemists and chemical engineers in their work on the Molecular Frontier.

In this report we have tried to show, illustrating our arguments with a series of challenges, that the fields of chemistry and chemical engineering are extraordinarily broad in their range, and that they include many important areas in which opportunities for research abound. We have purposely not tried to prioritize these areas and challenges. Is it more important to fight terrorism, to cure cancer, or to prevent the degradation of our environment? Is it more important to understand the chemistry of life or to refine theory to the point at which we can predict the exact substance that should be created for some desired property and then predict how to manufacture it? These all are critical to our future, and all are challenges for the chemical sciences. Thus we hope that the great range of opportunities in the chemical sciences will resonate with the interests of many young people making career choices, and with a society that needs to encourage their choices.

The Committee on Challenges for the Chemical Sciences in the 21st Century has attempted to view the roles and missions of chemistry and chemical engineering as broadly as possible. As we continue to push forward the frontiers of science, we will increasingly do so by working with our colleagues in other disciplines. In this way, the chemical sciences will be able to contribute in remarkable ways to an improved future for our country, for humanity, and for our planet. The astonishing developments in science and engineering during the 20th century have made it possible to dream of new goals that might previously been considered unthinkable. A few of these are listed here as grand challenges, building on the challenges that are listed at the head of each chapter of the report. In some instances they may be realistic immediate goals, while in other cases they may be achieved in a more distant future. We encourage our colleagues in chemistry and

chemical engineering to give serious thought to these challenges, and to produce the advances in fundamental and applied research that will so greatly enhance scientific understanding and human welfare.

### Some Grand Challenges for Chemists and Chemical Engineers

- **Learn how to synthesize and manufacture any new substance that can have scientific or practical interest, using compact synthetic schemes and processes with high selectivity for the desired product, and with low energy consumption and benign environmental effects in the process.** This goal will require continuing progress in the development of new methods for synthesis and manufacturing. Human welfare will continue to benefit from new substances, including medicines and specialized materials.
- **Develop new materials and measurement devices that will protect citizens against terrorism, accident, crime, and disease, in part by detecting and identifying dangerous substances and organisms using methods with high sensitivity and selectivity.** Rapid and reliable detection of dangerous disease organisms, highly toxic chemicals, and concealed explosives (including those in land mines), is the first important step in responding to threats. The next important step for chemists and chemical engineers will be to devise methods to deal with such threats, including those involved in terrorist or military attacks.
- **Understand and control how molecules react—over all time scales and the full range of molecular size.** This fundamental understanding will let us design new reactions and manufacturing processes and will provide fundamental insights into the science of chemistry. Major advances that will contribute to this goal over the next decades include: the predictive computational modeling of molecular motions using large-scale parallel processing arrays; the ability to investigate and manipulate individual molecules, not just collections of molecules; and the generation of ultrafast electron pulses and optical pulses down to x-ray wavelengths, to observe molecular structures during chemical reactions. This is but one area in which increased understanding will lead to a greater ability to improve the practical applications of the chemical sciences.
- **Learn how to design and produce new substances, materials, and molecular devices with properties that can be predicted, tailored, and tuned before production.** This ability would greatly streamline the search for new useful substances, avoiding consider-

able trial and error. Recent and projected advances in chemical theory and computation should make this possible.

- **Understand the chemistry of living systems in detail.** Understand how various different proteins and nucleic acids and small biological molecules assemble into chemically defined functional complexes, and indeed understand all the complex chemical interactions among the various components of living cells. Explaining the processes of life in chemical terms is one of the great challenges continuing into the future, and the chemistry behind thought and memory is an especially exciting challenge. This is an area in which great progress has been made, as biology increasingly becomes a chemical science (and chemistry increasingly becomes a life science).
- **Develop medicines and therapies that can cure currently untreatable diseases.** In spite of the great progress that has been made in the invention of new medicines by chemists, and new materials and delivery vehicles by engineers, the challenges in these directions are vast. New medicines to deal with cancer, viral diseases, and many other maladies will enormously improve human welfare.
- **Develop self-assembly as a useful approach to the synthesis and manufacturing of complex systems and materials.** Mixtures of properly designed chemical components can organize themselves into complex assemblies with structures from the nanoscale to the macroscale, in a fashion similar to biological assembly. Taking this methodology from the laboratory experimentation to the practical manufacturing arena could revolutionize chemical processing.
- **Understand the complex chemistry of the earth, including land, sea, atmosphere, and biosphere, so we can maintain its livability.** This is a fundamental challenge to the natural science of our field, and it is key to helping design policies that will prevent environmental degradation. In addition, chemical scientists will use this understanding to create new methods to deal with pollution and other threats to our earth.
- **Develop unlimited and inexpensive energy (with new ways of energy generation, storage, and transportation) to pave the way to a truly sustainable future.** Our current ways of generating and using energy consume limited resources and produce environmental problems. There are very exciting pros-

*continues*

pects for fuel cells to permit an economy based on hydrogen (generated in various ways) rather than fossil fuels, ways to harness the energy of sunlight for our use, and superconductors that will permit efficient energy distribution.

- **Design and develop self-optimizing chemical systems.** Building on the approach that allows optimization of biological systems through evolution, this would let a system produce the optimal new substance, and produce it as a single product rather than as a mixture from which the desired component must be isolated and identified. Self-optimizing systems would allow visionary chemical scientists to use this approach to make new medicines, catalysts, and other important chemical products—in part by combining new approaches to informatics with rapid experimental screening methods.
- **Revolutionize the design of chemical processes to make them safe, compact, flexible, energy efficient, environmentally benign, and conducive to the rapid commercialization of new products.** This points to the major goal of modern chemical engineering, in which many new factors are important for an optimal manufacturing process. Great progress has been made in developing Green Chemistry, but more is needed as we continue to meet human needs with the production of important chemical products using processes that are completely harmless to the earth and its inhabitants.
- **Communicate effectively to the general public the contributions that chemistry and chemical engineering make to society.** Chemists and chemical engineers need to learn how to communicate effectively to the general public — both through the media and directly — to explain what chemists and chemical engineers do and to convey the goals and achievements of the chemical sciences in pursuit of a better world.
- **Attract the best and the brightest young students into the chemical sciences, to help meet these challenges.** They can contribute to critical human needs while following exciting careers, working on and beyond the molecular frontier.

# 1

## Introduction

Chemistry and chemical engineering have changed very significantly since they were last reviewed by committees of the U.S. National Research Council. They have broadened their scope—into biology, nanotechnology, materials science, computation, and advanced methods of process systems engineering and control—such that much of what is done and taught in chemistry and chemical engineering departments is now quite different from the classical subjects. For this reason, it was important to review chemistry and chemical engineering again, describing both their current state and the challenges that lie ahead.<sup>1</sup> As will be seen, many of these challenges are already the subject of active research, while others should stimulate new research.

This report breaks new ground: research, discovery, and invention across the entire spectrum of activities in the chemical sciences—from fundamental, molecular-level chemistry to large-scale chemical processing technology—are being summarized together for the first time. We use the term *chemical sciences*, or occasionally *chemical sciences and engineering*, to represent the field in which all chemists and chemical engineers work. Chemistry was reviewed in 1965 by a committee led by Frank Westheimer, in a report with the title *Chemistry: Opportunities and Needs*.<sup>2</sup> In 1985 a team led by George Pimentel produced *Opportunities in Chemistry*.<sup>3</sup> *Frontiers in Chemical Engineering: Research Needs and Op-*

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<sup>1</sup>The committee's Statement of Task is provided in Appendix B.

<sup>2</sup>*Chemistry: Opportunities and Needs*, National Research Council, National Academy Press, Washington, D.C., 1965.

<sup>3</sup>*Opportunities in Chemistry*, National Research Council, National Academy Press, Washington, D.C., 1985.

portunities<sup>4</sup> was issued in 1988 under the leadership of Neal R. Amundson. Our ambitious integration of the entire range of chemical sciences into one report—presaged by the publication in 1992 of *Critical Technologies: The Role of Chemistry and Chemical Engineering*<sup>5</sup>—reflects the way the field has evolved, the synergy and strong couplings in our universities between research and education in chemistry and chemical engineering, and the way chemists and chemical engineers function in industry.

The structure of the disciplines of chemistry and chemical engineering is discussed in more detail in the next chapter, with the aim of further probing these couplings. Although the emphasis in this report is on an integrated, seamless view of the chemical sciences, we recognize the well-developed disciplinary structures of chemistry and chemical engineering, and the effects of such disciplinary structures on future developments.

The current state of integration between the two traditional aspects of the chemical sciences, chemistry and chemical engineering, is extensive. Ideas and progress in fields such as polymers, catalysis, bioscience and technology and many others respect no boundaries between traditional academic departments. Those working in applied areas quickly utilize advances in basic science, while discoveries and problems in applied chemistry and engineering often stimulate basic scientific investigations. Since the connections between discovery and application are so strong, both activities are described together in the succeeding chapters. It is also important to recognize the existing and emerging strong integration between the chemical sciences and other fields from biology to solid state physics to electrical engineering. As the discussion will show, basic and applied chemical science and engineering place the field in a central role in the world of science and technology.

The interaction between fundamental research and applications is not a linear, unidirectional one in which basic ideas are spawned in isolation and flow inexorably to important applications. A more realistic representation of the interaction, applicable to the chemical sciences, is the quadrant diagram of Stokes (Figure 1-1).<sup>6</sup> Neils Bohr and Thomas Edison, respectively, personify pure science and pure empirical invention. Stokes points to Pasteur's work in microbiology and Langmuir's work on surface chemistry as examples of practical problems that provoked a successful drive for deeper fundamental understanding. Such examples are abundant in the chemical sciences, particularly because of the strong historical couplings between chemistry and chemical engineering and also because of the research and development efforts of major chemical companies and

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<sup>4</sup>*Frontiers in Chemical Engineering: Research Needs and Opportunities*, National Research Council, National Academy Press, Washington, D.C., 1988.

<sup>5</sup>*Critical Technologies: The Role of Chemistry and Chemical Engineering*, National Research Council, National Academy Press, Washington, D.C., 1992.

<sup>6</sup>*Pasteur's Quadrant*, Donald E. Stokes, Brookings Institution Press, Washington, D.C., 1997.

RESEARCH IS INSPIRED BY:		Considerations of Use?	
		NO	YES
Quest for Fundamental Understanding?	YES	Pure basic research (Bohr)	Use-inspired basic research (Pasteur)
	NO		Pure applied research (Edison)

FIGURE 1-1 The quadrant model of scientific research.

the relationships they have had with universities. The main point of the quadrant model is that just as fundamental science is appropriately not always aimed at producing technology, neither does science always precede technology. The interactions between basic research and applications are dynamic and cyclical, with mutual feedback spurring greater discovery and innovation. The spirit of this statement permeates our report.

*Beyond the Molecular Frontier: Challenges for Chemistry and Chemical Engineering* presents an overview. Here we describe, in broad strokes, the general goals, accomplishments to date, and future plans of the chemical sciences. After some discussion of the structure of the field in Chapter 2, there is a sequence of five chapters (Chapters 3 through 7) on the fundamentals of the chemical sciences and technology: synthesis and manufacturing, chemical and physical transformations, analysis and control, theory and computation, and the interface with biology and medicine.

A series of workshops, organized in concert with this report, has focused in more detail on the areas of societal benefit to which the chemical sciences contribute. Each workshop, organized by a separately appointed committee, has produced its own report—particularly aimed at identifying opportunities in both basic and longer-term research. It is anticipated that these focused reports will motivate work in directions that can have profound impacts on our society. The areas addressed by these workshops are materials, energy and transportation, national security and homeland defense, information and communication, health and medicine, and environment. These topics are also chapters of the earlier BCST report, *Critical Technologies: The Role of Chemistry and Chemical Engineering*,<sup>7</sup> and are discussed in this report as well, in an overview fashion, in Chapters 6 through 11.

<sup>7</sup>*Critical Technologies: The Role of Chemistry and Chemical Engineering*, National Research Council, National Academy Press, Washington, D.C., 1992.

Dividing the enterprise of the chemical sciences strictly into fundamentals and areas of societal benefit cannot, of course, be done with any degree of purity, so every chapter has significant elements of both. This is particularly true in the sections on theory and computation (Chapter 6) and on the interface with biology and medicine (Chapter 7). We close in Chapter 12 with our vision of grand challenges for the chemical sciences.

Our report was greatly helped by suggestions and contributions from many individual chemists and engineers, who were asked to suggest major challenges for our fields. They are listed in Appendix C.

Recent reports and books, besides the direct ancestors of this report (the Westheimer, Pimentel, and Amundson reports noted above), have addressed aspects of the chemical sciences and engineering. In 1999, the Royal Society of Chemistry of Great Britain produced a fascinating book, *The Age of the Molecule*,<sup>8</sup> describing some of the outstanding achievements of chemistry in recent years. A report on the aims and needs of the future for the U.S. chemical industry was issued in 1996 with the title *Technology Vision 2020*.<sup>9</sup> The 1992 NRC report *Critical Technologies* was noted above, and several relevant reports have emerged from the NRC's Chemical Sciences Roundtable, including *Assessing the Value of Research in the Chemical Sciences*,<sup>10</sup> *The Impact of Advances in Computing and Communications Technologies on Chemical Science and Technology*,<sup>11</sup> and *Research Teams and Partnerships: Trends in the Chemical Sciences*,<sup>12</sup> The NRC's Board on Chemical Sciences and Technology has also produced several focused reports that addressed research opportunities in such areas as catalysis,<sup>13</sup> polymer science and engineering,<sup>14</sup> free electron lasers,<sup>15</sup> and computational chemistry.<sup>16</sup>

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<sup>8</sup>*The Age of the Molecule*, Royal Society of Chemistry, London, U.K., 1999.

<sup>9</sup>*Technology Vision 2020: The U.S. Chemical Industry*, The American Chemical Society, American Institute of Chemical Engineers, The Chemical Manufacturers Association, The Council for Chemical Research, and the Synthetic Organic Chemical Manufacturers Association, Washington, D.C., 1996.

<sup>10</sup>*Assessing the Value of Research in the Chemical Sciences*, National Research Council, National Academy Press, Washington, D.C., 1998.

<sup>11</sup>*The Impact of Advances in Computing and Communications Technologies on Chemical Science and Technology*, Report of a Chemical Sciences Roundtable Workshop, National Research Council, National Academy Press, Washington, D.C., 1999.

<sup>12</sup>*Research Teams and Partnerships: Trends in the Chemical Sciences*, Report of a Chemical Sciences Roundtable Workshop, Washington, D.C., 1999.

<sup>13</sup>*Catalysis Looks to the Future*, National Research Council, National Academy Press, Washington, D.C., 1992.

<sup>14</sup>*Polymer Science and Engineering. The Shifting Research Frontier*, National Academy Press, Washington, D.C., 1994.

<sup>15</sup>*Free Electron Lasers and Other Advanced Sources of Light: Scientific Research Opportunities*, National Research Council, National Academy Press, Washington, D.C., 1994.

<sup>16</sup>*Mathematical Challenges from Theoretical/Computational Chemistry*, National Research Council, National Academy Press, Washington, D.C., 1995.

In 1996, *Chemistry Today and Tomorrow: The Central, Useful, and Creative Science*<sup>17</sup> was written by Ronald Breslow, at that time the president of the American Chemical Society. Three books<sup>18</sup> by Philip Ball also merit specific mention: *Made to Measure: New Materials for the 21st Century*, *Designing the Molecular World: Chemistry at the Frontier*, and *Stories of the Invisible: A Guided Tour of Molecules*. All these efforts have aided the goal of conveying the immense importance of the chemical sciences and engineering to a broad range of readers. This report is intended to continue the tradition.

We hope that this overview will be of value and interest to many readers who want to know—and critically evaluate—the status and future goals of the many important sectors of the chemical sciences. We want readers to understand what the chemical sciences and engineering are aiming to do, and how close they are to achieving some of the goals. We want to provide insight into how the field should be measured against some of these goals. The chemical sciences have an ambitious agenda for the United States to maintain leadership in this important field and attract an appropriate share of the very best minds. It will be necessary for chemists and chemical engineers to produce major new discoveries, revolutionary new technologies, and important new additions to the quality of life for our society. The chemical sciences and engineering must also stand ready to play a major role in assisting our government and shaping its policies to benefit all of our population.

Finally, it is critical to recognize that this report is missing one serious component: the future discoveries that we do not see clearly from our present position. The history of science repeatedly shows that major discoveries open up whole new areas of understanding and of practical applications that were not anticipated. The aim of this overview is not to attempt to predict the future with great clarity but rather to be certain that the future is as rich and productive as it can be. But as we examine the future of our fields, there is one prediction we need to make: *Chemists and chemical engineers will come up with inventions and discoveries that are not encompassed in any such survey, and we will all say—why didn't we think of that?*

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<sup>17</sup>*Chemistry Today and Tomorrow: The Central, Useful, and Creative Science*, Ronald Breslow, American Chemical Society, Washington, D.C., 1997.

<sup>18</sup>*Made to Measure: New Materials for the 21st Century*, Philip Ball, Princeton University Press, 1997; *Designing the Molecular World: Chemistry at the Frontier*, Philip Ball, Princeton University Press, 1994; *Stories of the Invisible: A Guided Tour of Molecules*, Philip Ball, Oxford University Press, 2001.

## The Structures and Cultures of the Disciplines: The Common Chemical Bond

### **Some Challenges for Chemists and Chemical Engineers**

- Create new understanding of our physical world and use that understanding to produce a better world.
- Ensure that the traditional division of chemistry and chemical engineering into subdisciplines does not impede scientific and technological progress.
- Collaborate with scientists and engineers in other scientific disciplines to more easily advance science and technology.
- Consider the properties and behavior of organized interacting systems and processes, thereby responding to the trend of chemistry and chemical engineering to incorporate integrated, rather than reductionist, approaches.

The first chapter of this report emphasizes the strong coupling and integration across the spectrum of chemical sciences and engineering. However, both chemistry and chemical engineering have traditional subdisciplines that define undergraduate education, graduate student training, and some aspects of the research agenda. The aims of these subdisciplines must be understood as part of the overall picture of the present and the future of our field.

In chemistry, standard subdivisions are analytical, biochemical, inorganic, organic, physical, and theoretical. The subdivisions in chemical engineering are: applied chemistry, kinetics and reaction engineering, process systems engineering, thermodynamics and chemical property estimation, and transport processes and separations. These subfield categories are primarily used for pedagogical clarity and organizational management in academia, but they are not typically used in industrial chemical research and development. However, the subfield limitations as artifacts and tools should be recognized—these categories are separated by boundaries that are neither essential nor rigid. This report has a central theme that creativity and progress often, perhaps even usually, occur across such boundaries. Thus as chemical science and technology move forward, it will be appropriate to examine whether the traditional disciplinary substructure continues to serve the chemical sciences well, or whether it is an impediment to progress. Chemistry, as a recognized discipline, is much older than the recognized field of chemical engineering with that name.<sup>1</sup> However, this does not reflect the true history of the two fields. Humankind has been doing useful things with chemistry for a very long time—going back to ancient Egypt and even to prehistoric times—and applied chemistry is the ancestor of the modern discipline of chemical engineering.

Chemists seek to relate the properties of all substances, both natural and man-made, to their detailed chemical composition, including the atomic arrangements of all the chemical components. Chemists want to do this not only for existing substances but also for new substances that do not yet exist. For instance medicinal chemists make new substances as potential cures for disease. Understanding how the properties of substances are related to their molecular structures helps chemists and chemical engineers design new molecules that have the desired properties, allows them to develop or invent *new* types of transformations for carrying out the syntheses, and assists them as they design ways to manufacture and process the new substances.

Chemistry is still one of the natural sciences, but in a special and unusual way. Chemists want to understand not only the substances and transformations that occur in the natural world, but also those others that are permitted by natural laws. Consequently, the field involves both *discovery* and *creation*. Chemists want to discover the components of the chemical universe—from atoms and molecules to organized chemical systems such as materials, devices, living cells, and whole organisms—and they also want to understand how these components interact and change as a function of time. However, chemical scientists consider not just the components of the chemical universe that already exist; they also con-

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<sup>1</sup>The formal origin of chemical engineering as a discipline is considered to date to 1888 when it was introduced as an option in the chemistry department at the Massachusetts Institute of Technology (*Frontiers in Chemical Engineering: Research Needs and Opportunities*, National Research Council, National Academy Press, Washington, D.C., 1988, p. 11).

sider the unknown molecules and substances and interactions that *could* exist. Thus there is a field of synthetic chemistry, in which new molecules and substances and chemical transformations are created, rather than discovered in nature.

New chemical compounds—consisting of new molecules—are being created at the rate of more than one million each year. However, the number of possible molecules that are reasonably small and simple—about the size of a typical medicinal agent and composed of the same few common elements—exceeds the number of known compounds by a factor of well over  $10^{30}$ . The chemical sciences produce tangible benefit to society when someone designs and engineers the production of a new and useful substance. Clearly, there is much to do in the creation and understanding of molecules that do not yet exist, and in developing the novel transformations that will be needed to make them.

Chemical scientists are concerned with the physical properties of substances. Are they solids, liquids, or gases? How much energy do they contain? They are also concerned with chemical properties. Can they be transformed to other substances on heating, or with light? Can they interact with other substances; for instance, can they dissolve in water, and why? Can they react with other substances to undergo a transformation to something new? Thus, the chemical sciences are concerned with substances, with their transformations, both chemical and physical, and with the design and control of processes to achieve these transformations on scales of practical commercial and beneficial value to society. Chemical scientists seek to fully understand the detailed mechanisms of these transformations, and to measure the rates of reactions, and to build predictive models of reaction sequences and networks for process design and control.

As part of the overall goal, chemical scientists also want to understand the biological properties of both natural and man-made substances. This includes not only learning the detailed molecular structures of all the substances in living things, but also understanding the transformations that go on in the life process. They want to understand these properties of pure substances, and they want to extend that understanding to organized systems of substances—including those as complex as a living cell, a whole living organism, and the complex multichemical system that is the earth itself. Chemical science is integral to all of bioengineering and biotechnology. Biosystems, from molecular assemblies to cells to organisms, require insight from synthetic and physical chemistry as well as analysis of complex chemical networks if they are to be understood and exploited for the benefit of society.

Investigating a single compound, a single reaction, or a single process may well fall within the expertise of a single discipline or subdiscipline, but the situation is different when the investigations are extended to systems—full assemblages of related components that address the same function—or to processes, where integrated systems of operations work in concert to produce a product. Understanding, developing, and manipulating systems and processes often re-

quire the synergistic advantages of the entire range of the chemical sciences—from fundamental chemistry, to chemical engineering, and even to other advanced areas of science and technology—to create scientific understanding and benefit for society. Chemical engineers have concerned themselves with design, scale-up, and construction of large chemical systems and processes. This requires mastery of chemical and physical transformations of matter. Chemical engineers bring quantitative, analytical, and computational tools to the design and development of chemical operations, systems, and processes. Chemical engineers have also made enormous contributions to fundamental science.

The evolution of chemical engineering as a distinct discipline within the chemical sciences occurred, largely over the course of the 20th century, through a series of leading paradigms. Chemical engineering emerged from applied chemistry by introducing an organized approach to the design of chemical process systems for manufacturing chemical products. The paradigm of *unit operations*—the individual steps of an overall process—characterized chemical engineering in the first half of the 20th century. During this time, the chemical industry, especially in the United States and Germany, was being built into a leading, and thriving, productive economic force with power and stability. Impressive success in this period was exemplified by the creation of a robust industry to produce polymeric materials in large volumes by the 1940s—when 15 years earlier the mere existence of such large molecules was being questioned on fundamental chemical grounds.

In the 1950s, and over the next roughly 30 years until the 1980s, chemical engineering research improved, advanced, and made more efficient both the design process and the ultimate designs of chemical plants. Similar progress was made in the understanding of chemical and physical transformations through applications of applied mathematics and computation. Academic research produced major advances in mathematical modeling and analysis—based on rapidly emerging new information on chemical kinetics, reaction mechanisms, and transport phenomena. This progress changed the process-design endeavor—from one based predominantly on empirical experience embodied in heuristics and correlations, to a more reliable, quantitatively predictive activity. The design of refineries and other facilities for production of large-volume commodity products was enormously influenced by predictive models based on science and applied mathematics. The abstraction necessary to produce general models for design purposes, as well as the maturing of chemical engineering as an academic discipline, had the effect of divorcing chemistry from chemical engineering to some extent, relative to the earlier period during which chemical engineering had emerged as a branch of chemistry.

The application of new methods for chemical research in industry during this period was reinforced by several factors. These included steady hiring of university graduates, the engagement of many university faculty members in the chemical sciences as consultants, the substantial growth of research divisions in many

companies doing long-range research, and the mutual understanding and alignment of goals between universities and industry.

All of these factors began to change in the 1990s. Fundamental chemical research began to overlap with and penetrate chemical engineering to an unprecedented extent. This has been characteristic for interdisciplinary fields such as polymers, catalysis, electronic materials synthesis and processing, biological science and engineering, pharmacology and drug delivery, nanoscale science and engineering, and computational science and engineering. These fields of research have become not just accepted but actually central to both chemistry and chemical engineering departments, and they cut across the traditional subdisciplinary boundaries discussed in the first paragraph. The nature of the efforts of chemists and chemical engineers in these areas are sometimes difficult to separate in a meaningful or useful way. Some research emphasizes fundamental curiosity or solving puzzles of nature, some aims to test intriguing or provocative hypotheses, and some seeks to improve our ability to address technological or societal problems.

There is no doubt that chemistry and chemical engineering have reached a high level of integration across the entire spectrum of the chemical sciences. Chemists—who have traditionally worked at the end of the spectrum nearest to pure, basic research—are also aware of the societal and technological benefit of their work. Indeed, such benefits are commonly cited to justify the costs of the research. Furthermore, chemists are increasingly involved in constructing, analyzing, and using complex systems and assemblies, from cells to clouds, from energy production to earth systems. This merges naturally with the systems approach of engineering. Approaching the chemical sciences from the traditionally chemical engineering end of the spectrum, we find chemical engineers increasingly entering, and in some cases leading, in more basic fields of chemistry because more science input is needed to solve technological problems or because the tools of the chemical engineer are more suited to discovery in certain areas. The evolution toward integration in the chemical sciences is quite consistent with the idea that they are gravitating toward Pasteur's quadrant of Figure 1-1, in which the interplay between basic and applied research is more cyclical than linear.

A new kind of relationship is emerging between universities and industry in the chemical sciences, influenced in part by the Bayh-Dole Act of 1980, which allowed universities to retain intellectual property rights from federally funded research.<sup>2</sup> As large industrial organizations have fewer and smaller departments doing long-range or basic research, they look to universities both for fundamental research and for students. In contrast to previous decades, in which many compa-

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<sup>2</sup>For further discussion of this topic, see: *Research Teams and Partnerships: Trends in the Chemical Sciences*, National Research Council, National Academy Press, Washington, D.C., 1999; *Reducing the Time from Basic Research to Innovation in the Chemical Sciences*, National Research Council, National Academy Press, Washington, D.C., in press, 2003.

nies simply supported university research and teaching without looking for a specific return, current university-industry partnerships are often focused on specific shorter-term production of new data, knowledge, and insight. This has produced at least two identifiable trends in the nature of these relationships. In some cases, the interactions have become focused but strong—in terms of financial support of the academic partner from industry—enabling an unprecedented level of breadth and depth in concentration on subjects of mutual interest. In other cases, in order for university research to achieve technological or societal relevance, it has become necessary for university researchers to strike out on their own, to take promising leads from basic research and convert them into more fully developed technology. This means using research as a starting point and developing it into the seed of a start-up company. When large companies invest less in developing their own basic science, such start-up ventures become important in providing pathways that lead from discovery and invention to sources of new business development.

When taken together, the factors introduced in this chapter explain the motivation and rationale for this *integrated* report on challenges facing the chemical sciences, chemistry and chemical engineering. The chemical sciences will unlock our ability to understand the mysteries of our world—from new synthesis and catalysis to life itself. The chemical sciences will produce answers to our future energy needs and environmental challenges. The chemical sciences will produce the materials of the future, and they will produce practical biotechnology from biology. In this spirit, chemists and chemical engineers together are moving beyond the molecular frontier. The central challenge will be to create new understanding of our existing and potential physical world, and to use that understanding to produce a better world.

## Synthesis and Manufacturing: Creating and Exploiting New Substances and New Transformations

### **Some Challenges for Chemists and Chemical Engineers**

- Develop methods that will enable synthesis of all important molecules in reasonable yields using compact synthetic schemes, so that no useful compound is inaccessible to practical synthesis.
- Develop novel transformations that perform with the selectivities typical of enzymatic reactions, so that geometric factors are more important than the intrinsic reactivity of a molecule.
- Use computer methods to design important target molecules and design efficient ways to make them.
- Exploit combinatorial methods to discover important properties in synthetic materials.
- Design synthetic procedures that can be varied systematically for the purpose of optimizing specific properties of the reaction products.
- Understand fully the basic chemical and physical properties of surfaces, especially those of solid catalysts.
- Develop versatile and reliable synthetic methodologies for hard matter (microstructured materials such as nanoparticles and porous solids) that are as effective as those for synthesis of soft matter (complex organic and biomolecules).

- Synthesize new substances that can spontaneously self-assemble into complex organized systems with important properties.
- Incorporate enzymes, native or modified, as catalysts in the synthesis and manufacture of important materials.
- Devise good manufacturing processes—efficient and environmentally benign, producing no unwanted by-products, and using little energy—for all important products.
- Intensify manufacturing processes, so that compact chemical plants can make required amounts of product efficiently, safely, and with minimal environmental impact.

## GOALS

The long-term goal of the basic science in synthesis is to develop the ability to create all the substances and organized chemical systems and transformations that are possible under the limits of natural laws, not just those that occur in Nature. The importance of such an extension of Nature is clear in medicinal chemistry, for instance, but it is also part of the basic science of chemistry itself. In most cases, only enough of the new molecules will be created to permit an evaluation of their properties.

Of course, in reality new chemical substances are not synthesized at random with no purpose in mind—the numbers that have still not been created are too staggering for a random approach. By one estimate,<sup>1</sup> as many as  $10^{200}$  molecules could exist that have the general size and chemical character of typical medicines. Instead, chemists create new substances with the aim that their properties will be scientifically important or useful for practical purposes. As part of basic science, chemists have created new substances to test theories. For example, the molecule benzene has the special property of “aromaticity,” which in this context refers to special stability related to the electronic structure of a molecule. Significant effort has gone into creating new nonbenzenoid aromatic compounds to test the generality of theories about aromaticity. These experiments helped stimulate the application of quantum mechanical theory to the prediction of molecular energies.

Synthesis is achieved by performing chemical transformations, some of which are already known and some of which must be invented. Thus another goal of the basic science of synthesis is to invent new types of transformations, both because novel transformations are part of the universe of chemistry and also because they are the tools that make it possible to create interesting and useful new substances.

<sup>1</sup>A. W. Czarnik, *Accts. Chem. Res.* 1996, 29, 112-113.

As another part of this field, it is also important to invent overall strategies to achieve multistep syntheses involving a sequence of transformations. Knowing how to perform simple transformations is like knowing the legal moves in chess; achieving the synthesis of a complicated molecule requires the strategic combination of many simple transformations, just as winning at chess requires a strategy to combine a sequence of legal moves. Some of the achievements in synthesis have involved the invention of general strategies to attack particular classes of difficult problems. These efforts will be directed toward the synthesis of many kinds of substances with a variety of descriptions, such as organic and inorganic compounds, polymers and ceramics, and hard materials and soft materials.

A special aspect of synthesis is the synthesis of natural products, chemical compounds found in nature. For example, once the chemical structure of penicillin had been determined, synthetic chemists set out to make it from simple chemicals using nonbiological techniques—even though the mold makes it very well. A synthetic procedure for making penicillin would also provide the opportunity for making analogous compounds. The structure of penicillin represented a challenge because it could not be made by the chemical transformations then known. Thus both new transformations and new strategies had to be invented. In this case, the result then allowed chemists to use these new transformations to make other related antibiotics, which are now used commonly as medicines. However, the original impetus for the synthesis was more basic. When chemists saw a structure in a natural compound that was too challenging for the current synthetic methodology, they created new methods and strategies that helped fill the chemical universe with more effective tools.

The goal of applied chemistry and chemical engineering is to learn how to manufacture useful new substances. Exploratory chemists often use methods that produce only small samples of the new material and are not suitable for large scale manufacturing, so entirely new schemes of synthesis must be invented. Also, manufacturing equipment and processes have to be developed that meet all the other criteria—efficient high-yield processes with inexpensive starting materials, easy isolation of pure products, and no environmental problems. A further more basic goal is to develop the general principles that can be applied to solve new problems.

In both synthesis and chemical manufacturing there is a general need to develop separation methods as well as synthesis methods. Until every synthetic reaction is perfect—with respect to atom economy, so no side-products are formed, and by performing the reaction without added solvents or catalysts—it is necessary to isolate the desired product and purify it. This is one of the most expensive aspects of some manufacturing processes, particularly in pharmaceutical manufacture. Thus there are two goals related to separations. One is to learn how to isolate and purify the desired compounds with high efficiency, and the other is to develop synthetic processes that do not need such separations. For manufacturing, a further goal is to eliminate solvents or at least replace them with

harmless, inexpensive, and easily removed or recovered solvents. One interesting approach is to substitute water for organic solvents; another is to use unusual solvents such as supercritical carbon dioxide or even supercritical water. Synthetic transformations often involve adding catalysts, substances that direct chemical reactions along less energetic but more efficient pathways. Solid catalysts that can be simply filtered away, or retained in a reactor as the other components pass through, are also desirable.

Atom economy is a goal only relatively recently understood. If all the atoms in the reactants are found in the desired product, we say that there is excellent atom economy. However, in many chemical reactions additional products are formed containing some of the atoms of the reactants. This is true in displacement and elimination reactions. It is also true if the reaction is not perfectly selective, and additional undesired products are formed. In most cases, the extra chemicals produced in displacement or elimination reactions or in nonselective reactions must be removed, and disposing of them adds cost and the potential for environmental problems (see Chapter 9 for further discussion of related matters).

### PROGRESS TO DATE

Few known and thermodynamically feasible molecular structures are presently seen as impossible goals for synthesis. New transformations and effective strategies permit chemists to synthesize highly complex molecules, such as new natural compounds discovered in the continued chemical exploration of the natural world. Again, the point of such work is to develop new chemistry that permits an approach to structures of the type found in nature. This expands the power of chemistry and allows medicinal chemists to synthesize complex structures.

Synthetic efforts have also extended to compounds of theoretical and practical interest. A variety of novel cyclic, bridged, caged, interlocking, knotted, and otherwise topologically unusual structures have been prepared in both the organic and inorganic arenas. These studies have provided new insights into structure and reactivity: for example, new zeolitic materials have valuable properties as catalysts, and highly strained caged organic structures have shown intriguing energetic properties.

An interesting example is the work to synthesize the alkaloid strychnine. Robert Burns Woodward (Nobel Prize, 1965) was the first chemist to synthesize this very complicated structure, which has many places where the detailed spatial orientation of chemical bonds was important. The synthesis was accomplished by a team of students and postdoctoral associates that he directed. The world did not need a new source of highly toxic strychnine, which is widely available in nature, but the synthetic challenge required Woodward to develop new approaches to some synthetic problems. The general approaches—involving new reactions and new strategies—developed for strychnine and other biologically relevant molecules taught chemists how to tackle other challenging synthetic problems and

indicated the kind of complex molecule that was accessible through synthesis. Continuing developments of new strategies and new chemical reactions in the 1980s and 1990s led to several new syntheses of strychnine by other chemists, using less than half the number of steps of the original Woodward synthesis. Such work, expanding the tools of synthesis, has greatly increased our ability to synthesize useful medicines.

There are natural targets whose syntheses have important practical applications. For example, paclitaxel (marketed as Taxol by Bristol-Myers Squibb) is an anticancer compound originally isolated from the bark of a species of yew tree, but for a long time it seemed that natural sources would not be sufficient to meet the need. Consequently, many chemists developed synthetic approaches to paclitaxel from readily available materials, although these are not yet fully practical for manufacturing. The quest continues, and a semisynthetic route has been developed starting with a compound isolated from yew needles that can be harvested without destroying the tree. An alternative approach has employed plant-cell cultures in bioreactors to produce paclitaxel from yew needles (see Chapter 7 for discussion of related matters).

Some established methods to achieve particular transformations are not applicable in all situations, and some are not practical in large-scale manufacturing. Consequently, new methods are still being sought even for the simplest transformations. For example, the oxidation of an alcohol to a ketone or an aldehyde has long been performed in the laboratory by using certain compounds of chromium as the oxidant, but the aldehydes are themselves often oxidized further by the chromium reagents. Now, new oxidants have been developed that do not have this problem. Also, chromium oxidants are not practical in manufacturing. Their cost is high, and more seriously, the chromium-containing waste products are not environmentally tolerable. A better process for manufacturing would be to use the oxygen from air as the oxidant, resulting in water as a product. Catalysts for air oxidation already exist. However, it may be necessary to develop improved catalysts to perform this inexpensive and environmentally benign process.

This illustrates a general difference between the reactions used in manufacturing and those used in laboratory research. Whenever possible, manufacturing involves catalytic processes, with inexpensive reagents. In laboratory research, the immediate goal may be just to make a small sample of a new compound to determine its properties; consequently, there is less concern about the cost of reagents or the environmental effect that a large-scale version would create. The goal is to make the new compound as quickly as possible, to see if its properties make it worth manufacturing or simply to expand our basic knowledge.

Some manufacturing processes use the special properties of zeolites, inorganic substances that have interconnected cavities of well-defined size and shape. Reactions can be catalyzed inside the cavities, and they are normally selective for the shape of the substrate that can enter the cavities, and for the shape of the

products being formed. Selective absorption into the cavities also makes zeolites useful in separations.

Many laboratory syntheses of important structural types of compounds are too long or complex to work well in manufacturing. Chemists working in the process area are thus often engaged in inventing new approaches that use the most modern reactions, in order to develop compact synthetic schemes with small numbers of acceptable steps. The modern reactions that make this possible are being invented by chemists involved in basic discovery and creation, usually in universities. The pressure on industrial process chemists to develop practical schemes for manufacturing important products means that they do not normally have the time for the basic research that can lead to new chemical reactions.

How do synthetic chemists invent and create new reactions? After recognizing the challenge—a transformation that cannot be done easily with current methods—they look for inspiration in several places. One is biochemistry. If living cells already perform a transformation related to the desired one, it may be possible to invent an analog of the natural process—a biomimetic process. For example, in living cells there are enzymes that synthesize amino acids, and they do it with complete selectivity for the geometric orientation of the bonds. Chemists have now invented ways to do this without enzymes, but inspired by what is known about the natural process. For many practical purposes, the results are more useful and general for manufacturing.

Another inspiration comes from the chemists who study reaction mechanisms, learning how transformations occur (Chapter 4). The insights from such basic work often suggest new reactions that should be possible. For example, much work has gone on recently to understand the catalysis of chemical reactions by soluble complexes of certain metals such as palladium and platinum. They catalyze transformations, often of great importance in manufacturing, that otherwise may be impossible. Other work has helped us understand catalysis by metal particles, in which the special chemical properties of the metal surfaces play the key role. The insights from this work have stimulated the invention of other processes, while at the same time these applications have stimulated more work aimed at basic understanding. Work in synthesis is at least as important in showing chemists new parts of their universe as it is in solving practical problems.

Another important area is the use of photochemistry—chemistry that results from light absorption—to perform transformations that are not otherwise possible. The practical applications of photosynthesis were based on fundamental work to learn the new pathways that light absorption makes possible, but the work on these synthetic methods has also added to our basic understanding of the reaction mechanisms. The important natural process of photosynthesis also inspires some work in photochemistry, where the challenge is one of producing artificial photosynthetic systems that could use sunlight to drive the formation of energetic materials.

Finally, it is not possible to discount the component of intellectual creativity for such inventions. To quote George Bernard Shaw, "You see things; and you say, 'Why?' But I dream things that never were; and I say, 'Why not?'" Chemists looking at their universe often see that some parts are missing, and they set out to create them. For example, a Nobel Prize was awarded to Herbert Brown and Georg Wittig in 1979 for the invention of new types of useful transformations that were unprecedented in nature. This effort to create goes beyond chemical reactions and extends to molecules and organized molecular systems that originate in the imagination of an individual chemist.

A Nobel Prize to Geoffrey Wilkinson and Ernest O. Fisher in 1973 recognized their creation, and understanding, of a new class of substances—unrelated to anything found in nature—called metallocenes. Originally, these organometallic sandwich compounds (and their "open-faced" versions) were of interest purely as new occupants of the chemical universe, as if a new type of planet had been created in the astronomical universe. However, some versions of such sandwich compounds have been shown more recently to act as catalysts for very significant reactions, and they are now applied in the manufacturing of polymers.

Synthetic inspiration can come from an attempt to make drastic improvements in the properties of existing substances. For example, some metals and metal compounds become superconducting at extremely low temperatures. Superconductors are attractive materials because they conduct electricity without any loss caused by resistance below a characteristic transition temperature, although above that temperature they are poor electrical conductors (and some are even insulators). More practical, high-temperature superconductors, first developed by Johannes G. Bednorz and Karl A. Muller, a mineralogist and a physicist, have great current and potential uses throughout science, including chemistry and chemical engineering. For example, most modern nuclear magnetic resonance (NMR) instruments have electromagnets wound with superconducting wires. Once an electric current is started in the wires, the source of electricity is disconnected, and the current keeps flowing as long as the temperature is kept very low by cooling the magnet with liquid helium. There is a great effort to invent new materials that would be superconducting at higher and more easily attained temperatures. Recently chemists and other scientists have been able to create new superconducting materials based on inorganic ceramics, which have considerably higher superconducting transition temperatures than the materials of Bednorz and Muller.

Since synthesis is such a central part of chemistry and chemical engineering, many other Nobel Prizes have recognized synthetic achievements. For example, a Nobel Prize in 1990 went to Elias J. Corey both for his contributions to the development of theory and methodology in organic synthesis and his application of them to the synthesis of important biologically active substances. It also recognized his formalization, and even computerization, of the strategies that successful multistep syntheses follow. Karl Ziegler and Giulio Natta received a Nobel

Prize in 1963 for inventing a new general method to synthesize important polymers, a method that uncovered much new basic science. A Nobel Prize in 1984 went to Robert Bruce Merrifield for his invention of a general approach to the synthesis of polypeptides and proteins, in a style directly reminiscent of the biological method used in such synthesis.

Although much of the preceding discussion involved the synthesis of new molecules by organic and inorganic chemists, there is another area of chemistry in which such creation is important—the synthesis of new atoms. The periodic table lists elements that have been discovered and isolated from nature, but a few have been created by human activity. Collision of atomic particles with the nuclei of existing atoms is the normal source of radioactive isotopes and of some of the very heavy elements at the bottom of the periodic table. Indeed nuclear chemists and physicists have created some of the most important elements that are used for nuclear energy and nuclear weapons, plutonium in particular.

An exciting goal has recently shown signs of progress. Theory has suggested that beyond the bottom of the usual periodic table, where the elements become quite unstable and have only a fleeting existence, there should be an “island of stability,” a group of elements more stable to nuclear decay than those coming earlier in the periodic table. Recently nuclear chemists have obtained evidence for such special stability in the predicted elements. They are not stable enough for long-term isolation, but their properties help confirm theories of nuclear structure and stability.

## CHALLENGES AND OPPORTUNITIES FOR THE FUTURE

There is a healthy integration of the various branches of chemistry and chemical engineering. This integration brings together synthesis and measurement, theory and experiment, and design and manufacturing. The integration extends to the related disciplines with which chemistry and chemical engineering share the intellectual frontiers of science and technology—biology, physics, and electronics to name just a few. This has opened great new opportunities.

Within chemistry, synthetic chemists will increasingly make use of the special properties of metal-based catalysts, both solid and as soluble complexes, to devise new transformations that are selective and efficient. Chemical engineers are increasingly involved in product design, in addition to process design, requiring the integral participation of the chemical engineer in the molecular conception and design of the products. Physical chemists and chemical engineers will increasingly understand the surface chemistry and properties of solid catalysts; that understanding will help in the design of even better catalysts. Inorganic chemists will create many new types of molecules that combine inorganic and organic components, and that have applications and interest in both inorganic and organic chemistry. Chemical reactor modeling has advanced the field of electronic materials production significantly.

Theoretical chemists will increasingly be able to predict the properties of unknown molecules, and thus stimulate synthetic chemists to make the interesting ones. As chemical engineers open new frontiers in biological engineering, they team effectively with chemists and biologists to influence biosystems and processes from metabolism to cell adhesion. The synergy with biology is particularly strong in medicinal chemistry, where computer methods are used to design drugs. In every pharmaceutical company the computer-aided-design group works from the molecular structure of an important protein, that had been determined by structural chemists, and guides and rationalizes the work of the synthetic groups. Some important new medicines have been designed this way, and many more will come in the future.

### **Development of New Synthetic Methodology**

In spite of the impressive progress achieved by synthetic chemists in the past several decades, the state of the art of methods for chemical synthesis remains at an early stage of development. There is a great need for new reactions and synthetic methods to permit any substance, of any complexity, be it organic or inorganic in structure, to be synthesized with high chemical efficiency, in a small number of steps, and with minimal cogeneration of any waste products. Synthetic methodology is the software of the chemical sciences. Just as there is an explicit expectation that there will be a constant evolution and improvement of the software and the operating systems that drive our computers, so should the chemical community expect that there will be constant improvement and evolution of the armament of methodologies available for the practicing preparative chemist and the chemical industries. An explicit goal of the chemical community should be to make continual improvements in synthetic methodology, thereby expanding the range of challenging molecules that are accessible to practical synthesis.

### **Catalysis**

Some aspects of synthetic chemistry have changed in response to environmental needs. For example, in the pharmaceutical industry the classical methods produce, on the average, about nine times as much disposable waste as desired product. This has led to the demand for procedures that have atom efficiency, in which all the atoms of the reacting compounds appear in the product. Thus (as discussed earlier) the demand for atom economy offers additional opportunities for creative invention of transformations.

There are still numerous major important targets for synthesis. As a simple example, we currently manufacture ammonia—for use in fertilizers and other important products—by causing nitrogen to react with hydrogen at high temperature and pressure. Yet microorganisms in the roots of some legumes are able to convert nitrogen to ammonia at ordinary temperatures and pressures (although

not using gaseous hydrogen). We need to understand their chemistry, even if it is not as practical as is our current method of manufacturing ammonia. Similarly, the enzyme methane monooxygenase is able to use atmospheric oxygen to convert methane to methanol, whereas chemical systems tend to oxidize the methane further. We need to develop catalysts for this important process that could convert the methane in natural gas into a useful chemical. The catalysts for both of these processes will surely include the inorganic chemistry of metallic elements.

### Combinatorial Chemistry

Some new aspects have been introduced into the style of synthesis recently, and these aspects hold great promise. One has to do with what are called *combinatorial* methods, where syntheses are carried out to make many different (but related) products at one time. Sometimes these are in a mixture, but with the different products attached to separate polymer beads, while at other times the simultaneous reactions are performed in many different small vessels. For example, a library of amide products might be produced by allowing a single reagent to react with a large group of different amines. For such libraries of products, different schemes have been devised to identify the individual components. Then the various products can be tested for a desirable property. In pharmaceutical chemistry, the library of products is put through biological screens, usually automated, to determine whether any of the products binds particularly well to an enzyme of interest or to another biological receptor. When one product has been identified as a good binder, normal synthetic procedures are used to make enough for thorough testing.

At one time, some people predicted that the ability of combinatorial methods to produce literally thousands of new products at one time would diminish the need for synthetic chemists in the pharmaceutical industry. However, the opposite has turned out to be true. The large number of leads produced by combinatorial methods requires many more synthetic chemists to continue research on these compounds in a more traditional way. Companies are increasing, not decreasing, their cadre of synthetic chemists. In addition, combinatorial methods have provoked radically new approaches to screening the libraries rapidly for good lead compounds, generating a new field called high throughput analysis and new opportunities for chemists.

### Biomimetic Synthesis

As we increasingly understand the chemistry performed by living systems, in particular that catalyzed by enzymes, we will continue to develop biomimetic methods to achieve some of the special selectivities that enzymes show. Enzymes can selectively bind a particular molecule out of the mixture of substances in the cell, then hold it in such a way that the geometry of the enzyme-substrate com-

plex determines what happens next in a sequence of chemical reactions. For example, in an enzyme-substrate complex the reaction may take place at a particular part of a molecule even if that is not the most chemically reactive site—in contrast to normal synthetic chemistry, where changes take place at the reactive functional groups. Alternatively, enzymatic reaction might produce just one of several possible stereochemical consequences. For example, an enzyme might bind a natural L-amino acid but not the mirror image and thus distinguish the L -amino acids that human cells contain from the D-amino acids sometimes found in bacteria.

The selective introduction of chirality is a problem of much current interest in synthesis, and it is generally solved by using the same concept that governs enzymatic reactions. The nonchiral substrate interacts with a chiral reagent or catalyst, and the selective conversion of the substrate to a chiral product follows. Pioneering work to develop such methods was recognized in 2001 by Nobel prizes to William S. Knowles, Ryoji Noyori, and K. Barry Sharpless. In synthesis the binding often involves quite different forces than are used in enzymes, and the reagents and catalysts are much smaller than are protein enzymes. New procedures increasingly involve the formation of well-defined molecular complexes between substrate and catalyst, or substrate and reagent, that may allow chemists to overcome the classical domination of selectivity by the reactivity of functional groups. Donald J. Cram, Jean-Marie Lehn, and Charles J. Pedersen received Nobel prizes in 1987 for their work on molecular complexes.

There is another approach that is increasingly part of synthesis: the use of enzymes as catalysts. This approach is strengthened by the new ability of chemists and molecular biologists to modify enzymes and change their properties. There is also interest in the use of artificial enzymes for this purpose, either those that are enzyme-like but are not proteins, or those that are proteins but based on antibodies. Catalytic antibodies and nonprotein enzyme mimics have shown some of the attractive features of enzymes in processes for which natural enzymes are not suitable.

### Self-Assembly

Historically, chemistry has been largely reductionist, breaking natural materials such as wood down to their pure components so they could be analyzed. It has since become more integrationist, putting together pure chemicals into complex organized structures. This is true in the new areas of nanoscience and nanotechnology, where synthesis is needed to make organized arrangements of many chemical components—nanostructures—with the distant goal of making tiny molecular machines and even molecular scale computers. Integration is also exploited as chemists begin to synthesize organized structures that imitate some of the properties of living cells. The processes carried out by living cells depend on the spatial organization of many different chemical components. Chemists, in

particular synthetic chemists, also need to start building such organization into structures with many different cooperating chemical components—both to understand them and to create useful microscopic devices. Such organization is most favorably based on spontaneous self-assembly of the chemical components, driven by their own selective molecular recognition and interactions. This is as if the components of an automobile would automatically fall into the correct places, rather than being placed there by machines. In chemistry such spontaneous self-assembly is possible on the molecular scale, but needs to be developed.

A vital aspect of chemical self-assembly is *selection*. In a mixture of compounds the correct pairings of chemicals must occur, so the system must have a way to choose those correct pairings. An exciting new challenge is to develop ways to impose a process of selection on the mixture of components, so that unwanted interactions are suppressed. In biology mutants are selected because they convey an advantage to a cell. Chemists need a similar tool, for example a library of possible catalysts from which the system would use their relative catalytic activities to self-select the one that is the most potent. This would remove the current need to screen the entire library for such activity. An even more desirable goal, difficult to reach currently, would be to develop chemical systems that could vary their own structures in a drive to produce the optimum of some desired property such as catalytic potency or strength of binding to a receptor. Such a chemical system could optimize itself according to the needs of humankind.

## Manufacturing

Chemical manufacturing systems involve the implementation of chemical synthesis schemes to transform one composition of matter to another on scales from the very small (micrograms) to very large (hundreds of billions of kilograms per year). These materials and processes enable modern life. They may be inorganic, organic, or even biological, and they span the range from metals and concrete to glass, paper, and plastic; from advanced composites and electronic materials to fertilizers, agrochemicals, and dyes; from drinking water and fuels to safe refrigerants; and from pharmaceuticals to packaging for secure nuclear wastes. No matter what composition is produced, no matter what the purpose, and no matter what the scale, process systems engineers face relentless demands. These demands are for increased capital efficiency and reduced costs for materials, labor, and energy—all while producing material of high and consistent quality and doing so reliably, safely, sustainably, and with minimal environmental impact.

Specific new challenges to process systems engineering are both economic and social. Globalization of the chemical enterprise has opened new markets that are linked to the general increase in the standard of living throughout the world. At the same time, globalization has resulted in growing worldwide competition. This, along with the introduction of electronic commerce, is producing greater market efficiencies. It is also producing reduced manufacturing margins at a time

of increased investor demands for predictable earnings growth, despite the inherent cyclical character of very-large-scale capital-intensive industry.

Sustainability, hazard reduction, and protection of health and the environment remain great concerns for the process industries. Many of the raw materials used—especially those derived from oil, gas, and some plants and animals—have been and in some cases continue to be depleted at rates either large compared to known reserves or faster than replenishment. In addition, there is the desire for products, intermediates, solvents, catalysts, and other materials produced or selected for use in chemical manufacture to be as safe and nontoxic as possible during their use and to be recoverable or benignly degradable after their use.

Also, by the very nature of chemical transformations, there are almost always unused chemicals remaining. These chemical leftovers include contaminants in the raw materials, incompletely converted raw materials, unavoidable coproducts, unselective reaction by-products, spent catalysts, and solvents. There have long been efforts to minimize the production of such waste products, and to recover and reuse those that cannot be eliminated. For those that cannot be reused, some different use has been sought, and as a last resort, efforts have been made to safely dispose of whatever remains. The same efforts apply to any leftovers from the production of the energy from the fuels produced or consumed by the processing industries. Of particular immediate and increasing concern are the potential detrimental effects of carbon dioxide emissions to the atmosphere from fossil fuel combustion, as discussed further in Chapters 9 and 10.

The chemical enterprise must meet the societal and environmental challenges it faces. This will necessitate starting from different raw materials, producing new products, using new sources of energy, and paying much greater attention to the creation and disposal of waste. Taking these steps will require innovations in the chemistry used, in catalysts to facilitate this chemistry, in reactors to manufacture the products via this new chemistry, and in separations techniques to purify the resulting products and recover everything else.

The future will likely see greater use of more abundant or renewable raw materials, and greater reuse of materials such as carbon dioxide, salts, tars, and sludges that are currently discarded as waste. Exploiting some of these alternative raw materials and chemistries may involve greater energy input than required for raw materials presently in use, and the source and impact of any such increased energy requirements will need to be carefully considered. Many of these goals are incorporated in the principles of green chemistry.<sup>2</sup>

Chemistries such as gasification, carboxylation, carbonylation, partial oxidation, and salt splitting may see much greater emphasis in manufacturing. These chemistries will need concurrent development of more selective catalytic and biocatalytic systems and promoters, as well as processes requiring much less ex-

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<sup>2</sup><http://www.acs.org/>.

otic materials of construction than we now have available. Demands for greater capital, energy, and material efficiency will require the development of process systems that are more tightly integrated. Such systems will need greater mass and energy recycling, more by-product reuse, and advances in computer-aided, plantwide process control. Only with such advances will it be possible to maintain safety, reliability, flexibility, operability, and economic performance in highly integrated systems.

Some of the new process engineering technologies for manufacturing will involve new devices and the exploitation of new phenomena that will change the traditional way we look at unit operations in chemical engineering. In the area of reaction engineering, new units might include centrifugal or high shear reactors, very short contact time reactors, or rotating packed-bed reactors. In these units, process intensification (see box) is often a major driving force for reducing the size of the device or equipment. Other novel reactor technologies include microwave reactors that have the objective of reducing the energy use and bulk temperature of reaction mixtures by performing selective heating on the particles of the catalyst. Novel separations technologies include membrane absorption and membrane distillation, centrifugal distillation columns, and simulated moving bed adsorbers.

An interesting trend in process intensification is not only the reduction in the size of equipment, but the integration of different functions and phenomena. For instance, microreactors are devices of very small dimensions that have a structure consisting of different layers with micromachined channels (10 to 100 microns in diameter). The layers perform different functions such as mixing, catalytic reaction, heat exchange, and separation. The very high heat-transfer rates (e.g., 20,000 W/m<sup>2</sup>K) allow exothermic processes to be operated isothermally. Also, very low reaction-volume/surface-area ratios make microreactors attractive for processes involving highly toxic components.

Process intensification also can be achieved by reconfiguring standard equipment. A good example is the use of divided wall columns for distillation, in which various separations that are commonly performed in separate columns are integrated into one single column. This is accomplished through clever rearrangement of trays and divisions between them, yielding significant savings in both capital cost and energy. Another way of achieving process intensification is by expanding the functions in the device. An example is reactive distillation in which hold-up catalyst is added over a subset of trays in a column to perform simultaneous reaction and separation. The methyl acetate column developed by Eastman Chemical (see box) provides an excellent illustration of the dramatic cost reductions that can be achieved with this technology. Specifically, a single reactive distillation column replaced a large complex plant that consisted of one reactor and nine conventional columns. This not only reduced the required capital investment to one-fifth of the original cost, but it also greatly reduced the energy consumption.

Demands for greater capital, energy, and material efficiency will require the development of more integrated process systems involving greater mass and energy recycle, as well as advances in computer-aided process control to maintain safety, reliability, flexibility, and operability in such highly integrated systems. Capital efficiency will also drive the need for greater process intensification as discussed above, making more material more quickly and in less space. New methods will need to be developed exploiting new phenomena to increase the intrinsic rates of mass transfer (for reactors and separations devices), heat transfer (again associated with separations and reactions devices), and reaction kinetics. In addition, the synergistic combination of multiple tasks into single devices such as reactive distillation will become more widespread. Such advances could result in new reactor configurations and new separations and other processing equipment exploiting different phenomena than at present, resulting in smaller, simpler, less energy-demanding processes, and less environmental impact.

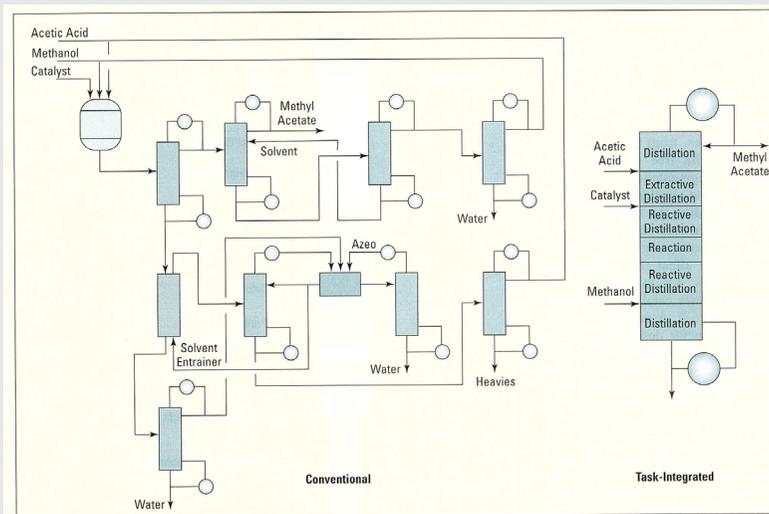
### **Emerging Platforms for Process Intensification and Miniaturization**

Chemical engineers have responded successfully for years to pressures to improve the efficiency and reduce the cost of chemical process operations and to design and construct chemical plants as safely and expeditiously as possible. In this regard, the unit operations concept has long been a useful organizing principle for the synthesis of chemical process flow sheets, while economies of scale and energy efficiency have dictated construction of the very large petrochemical plants that have dominated the scene for decades.

However, this situation is hardly static. For instance, hybrid process methods and apparatus for performing chemical operations in a highly integrated fashion are continually being introduced that defy simple classification according to the traditional unit operations scheme—and render somewhat naive the view of the process flow sheet as an orderly network of discrete and well-defined steps. At the same time, the mix of technical, economic, and social factors that drive chemical plant siting, design, and capacity decisions is continually evolving to reflect emerging social issues related to environmental acceptability and public safety, especially where the transportation, storage, and use of hazardous chemicals are concerned. Bigger is not necessarily better, and the future may conceivably witness the construction of smaller, modular, less centralized, and more flexible chemical plants capable of “on-demand” chemical production.

Several technological responses to these emerging trends can be gathered under the umbrella of process intensification. This term encompasses a wide range of methods and equipment for performing chemical processing steps more quickly and compactly, thereby increasing the

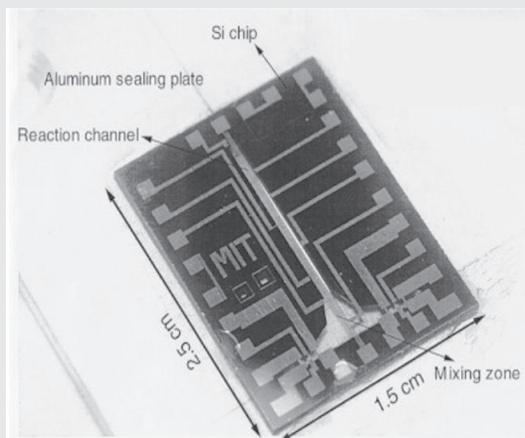
volumetric productivity and reducing the footprint of the chemical plant. Efforts at process intensification, underway for several decades, have focused primarily on downsizing process equipment and boosting its throughput; static-mixer-based devices, compact heat exchangers, structured packings, catalyst monoliths, and centrifugal contactors have all been used for this purpose. In recent years, considerable energy has also been devoted to the design of multifunctional apparatus capable of conducting several process steps in a synergistic fashion. Such task integration is exemplified by the reactive distillation process for methyl acetate production.



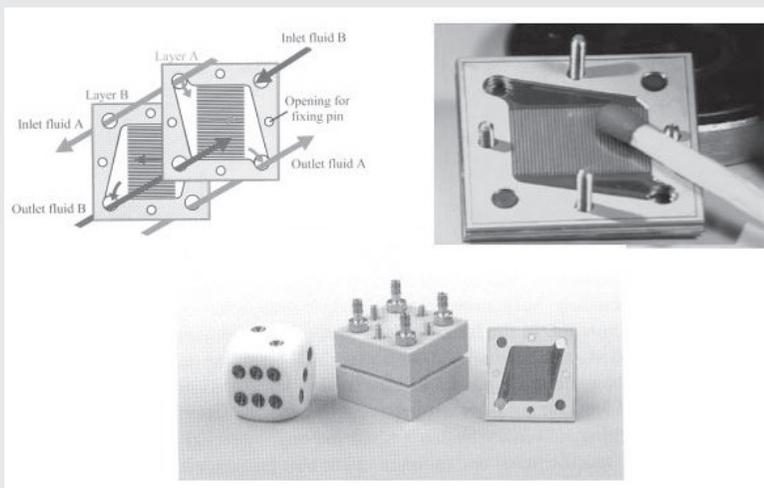
The task-integrated methyl acetate column is much simpler than a conventional plant. Courtesy of Eastman Chemical Company.

A family of approaches to achieving high volumetric productivity that is receiving considerable attention in this age of miniaturization involves the use of apparatus with very small flow channels with dimensions of several microns and up. The steep concentration and temperature gradients realized in such equipment encourage rapid heat and mass transfer and promote greater uniformity of reaction conditions. Not only the rate but also the selectivity and yield of chemical conversions can, in principle, be significantly improved. Devices based on both silicon chip and micro-channel architectures are currently being considered for performing rapid mixing, heat-exchange, and catalytic reaction in a highly compact and intrinsically safe manner.

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The silicon chip as a miniaturized chemical reactor. Courtesy of Felice Frankel.

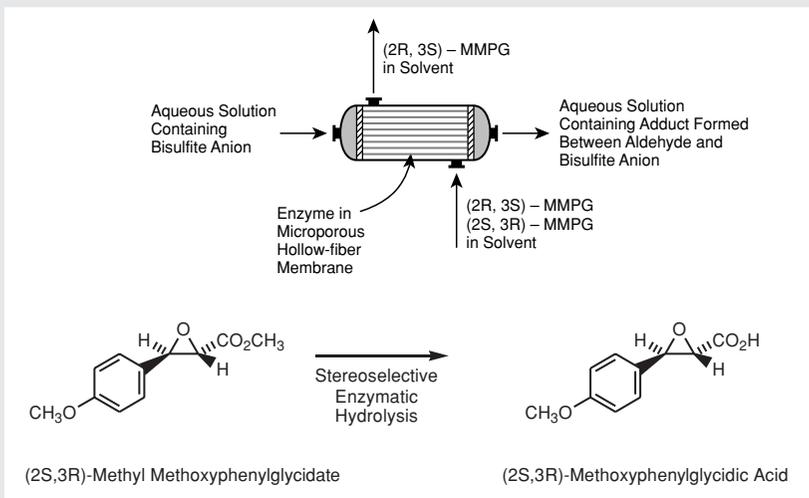


Micro heat exchangers based on microchannel architecture. Top left and bottom: Reprinted with permission from W. Ehrfeld et al., *Microreactors: New Technology for Modern Chemistry*. Wiley-VCH: Weinheim, Germany, 2000. Top right: Courtesy of the Institut fuer Mikrotechnik Mainz, GmbH.

Chemically functional membranes afford yet another intriguing platform upon which process-intensified chemistry can be performed. For example, an enzyme membrane reactor process is used to produce a

chiral intermediate for the cardiac drug diltiazem. This membrane system performs a number of tasks in a highly integrated and effective fashion including:

- reversible biocatalyst immobilization;
- minimization of mass transfer resistance through efficient substrate/enzyme contact;
- separation of immiscible organic and aqueous process streams, along with separation of the reactants and products contained within them; and
- coupling of the enzymatic reaction with a subsequent complexation reaction designed to remove an inhibitory by-product in the form of a water-soluble adduct.



Enzyme membrane reactor for production of diltiazem intermediate. A solution of the racemic ester in organic solvent enters the port at the bottom of the reactor and flows past the strands of microporous, hollow-fiber membrane that contain an enzyme. The enzyme catalyzes hydrolysis of one enantiomer of the ester that undergoes decarboxylation to 4-methoxyphenylacetaldehyde (which in turn forms a water-soluble bisulfite complex that remains in the aqueous phase). The other enantiomer of the ester remains in the aqueous stream that leaves the reactor via the port at the top. Courtesy of Sepsacor, Inc.

Still other types of chemically functional membranes—particularly adsorptive microfiltration membranes containing affinity ligands or other complexants bound to interior pore wall surfaces—are capable of

*continues*

dramatically downsizing adsorptive separation equipment. Operation of these so-called “affinity membranes” in a flow-through mode sidesteps the rate-controlling diffusive mass transfer resistances characteristic of particulate adsorbents used in packed beds—and so improves volumetric productivity. Interestingly, nature abounds with examples of process intensification realized with the aid of adsorptive membranes and enzyme membrane reactors.

### WHY ALL THIS IS IMPORTANT

The most distinctive aspect of the chemical sciences and engineering is the ability to create new molecules and chemical systems—from minute to commodity quantities—without being limited to the study of those that already exist in nature. The expansion of our chemical universe through synthesis leads to great new scientific insights. Moreover, chemical synthesis is the activity that has made chemistry and chemical engineering so vital to human health and welfare. The opportunities and challenges for the future are unlimited. The promise of better medicines and better materials depends on the ability of synthetic chemists to create new transformations and to use them in the creation and manufacture of new substances. It is no surprise that synthesis is still the active concern of a large fraction of practicing chemists, and will remain so.

The development and implementation of techniques will be critical for all aspects of chemical manufacturing—from synthesis and analysis to optimization, evaluation, design, control, supply-chain management scheduling, and operation of chemical process systems. This will need to be done in a way that is consistent with societal and economic objectives and constraints. And it will be critical no matter what the chemistry or biochemistry, whether isolated or in supply-chain networks, dedicated or general purpose, batch or continuous, microscale or macroscale. These constraints will require the further creation and exploitation of a science base that includes novel representations of the underlying chemical and physical phenomena. Similarly, it will demand computationally efficient formulation and solution methods, as well as the expansion and incorporation of advanced process systems engineering expertise and judgment.

# Chemical and Physical Transformations of Matter

## **Some Challenges for Chemists and Chemical Engineers**

- Perfect the tools to study reaction mechanisms of chemical and biochemical reactions, so the processes can be observed directly and more efficient syntheses can be designed rationally.
- Develop reliable computer methods to predict the detailed pathways and rates of unknown chemical reactions, avoiding the need for creating and measuring them to determine their practicality.
- Understand the chemistry and properties of large molecules, including biopolymers, to the level that small-molecule chemistry is understood.
- Understand the behavior of molecules and substances in unusual environments: at extreme temperatures or pressures, absorbed on solid surfaces, or under shear flow.
- Understand the chemistry of molecules and substances in their excited states, or at or near their critical points, and at the nanoscale level in which surface characteristics can dominate bulk properties.

## **GOALS**

A principal goal of the chemical sciences is to understand and manipulate chemical and physical transformations of matter. We are using the term transfor-

mation very generally here to mean a change in composition, state, or organization of matter, or movement or rearrangement of material by flow, heat or diffusion, which describes the very essence of chemical science and technology. We need to understand the mechanisms of chemical reactions that we invent, as well as the transformations that occur in living systems and in the environment. Such an understanding will aid in the design of new transformations.

In this domain of transformations of matter, the full scope of the chemical sciences—from basic to applied to technological innovation—is easily seen. For example, it is a fundamental challenge to understand how efficient catalysts, such as nature's enzymes, are able to perform transformations with very high speeds and selectivities. Such insight would be useful in applied chemistry to design catalysts or conditions for the transformations. Catalysis has been key to a large number of new chemical products and processes in the last half century. Catalytic chemical reactors are the central elements in chemical process systems in which thermodynamic phase behavior, flow, heat transfer, and diffusion all play key roles in performance. Many processes arising in chemical science and technology involve physical transformations in addition to, or even without, chemical reactions, such as phase change, polymer and particulate processing flows, or diffusion in liquids, solids, and membranes. This chapter provides an overview of chemical and physical transformations of matter that are the heart of the chemical science enterprise.

### PROGRESS TO DATE

A chemical transformation can occur when molecules collide with sufficient energy. Typically, reaction happens when the molecules are heated or irradiated to provide the energy necessary to overcome the activation barrier that separates reactants from products. A catalyst reduces the magnitude of the activation barrier by changing the pathway of the reaction. As described in Chapters 3, 7, and 10, catalysis is fundamental to biology, to synthesis, to manufacturing, and to energy saving and generation.

Many intermediates along the path of a reaction cannot be directly observed with current instrumental technology, making this objective one of the long-standing goals of the chemical sciences. In 1999, Ahmed Zewail received the most recent of the several Nobel Prizes recognizing developments of methods to follow fast reactions. He was able to witness the bond-breaking and bond-making process on the time scale of  $10^{-15}$  seconds, which some say is the limiting time scale for chemical reactions. In 1994, George A Olah received a Nobel prize for work establishing the properties of reactive carbon cations, which are intermediates in many important transformations.

Whereas the detailed molecular structures involved throughout the entire procession from starting materials through the transition states to products in a chemical reaction are so far not directly observable, there are certain classical ways in

which reaction mechanisms are effectively deduced. One route is through the use of kinetics, the observation of how the rate of a reaction depends on concentrations of its various components, and on temperature and sometimes pressure. If the rate doubles when either of two reactants is doubled in concentration, we know that both are together in the transition state, while if the reaction speeds up as the pressure is increased we know that the system has a decreased volume at the transition state. Chemical kinetics studies can also facilitate the design of chemical reactors and processes.

A related technique for revealing mechanisms measures the rates of related reactions, using reacting molecules that differ in a small way from each other. A classical approach involves measurement of isotope effects. For example, when a hydrogen atom in a reactant is replaced by a deuterium atom, the isotope with twice the mass, the rate of the reaction will be affected depending on what that hydrogen atom is doing at the transition state. This technique has contributed to our knowledge of mechanisms for a large number of reactions and has been particularly useful in exploring the mechanisms of enzyme reactions. Enzymes will often have such strict geometric requirements that significant changes in the size of the substrate can change the rate for geometric reasons. However, the change from hydrogen to deuterium does not involve such a geometric problem.

One interesting feature of the hydrogen versus deuterium rate effect is that it can be used to detect a very special phenomenon—quantum mechanical tunneling by the hydrogen. In this process, the hydrogen essentially disappears from one position and then reappears a short distance away without traversing the intermediate space. This is possible because all atoms have the character of both a particle and a wave, and waves can diminish in one spot and build up in another without necessarily rolling across the intervening region. Such tunneling has been demonstrated in some enzymatic reactions and invoked to help explain their very high rates. More detailed understanding of quantum mechanical phenomena is essential to a clearer picture of chemical reaction mechanisms and rates.

Evidence on the mechanism of reactions can also come from examining the exact molecular geometry of the overall process, its stereochemistry. For example, if a reactant with defined handedness (chirality) is converted to a product that is an equal mixture of the left- and right-handed forms, the loss of handedness indicates that a particular geometry must have been involved along the path. If a right-handed molecule is converted only to a left-handed product, we say that an inversion of configuration has occurred, and this also tells us a lot about how the reaction occurred.

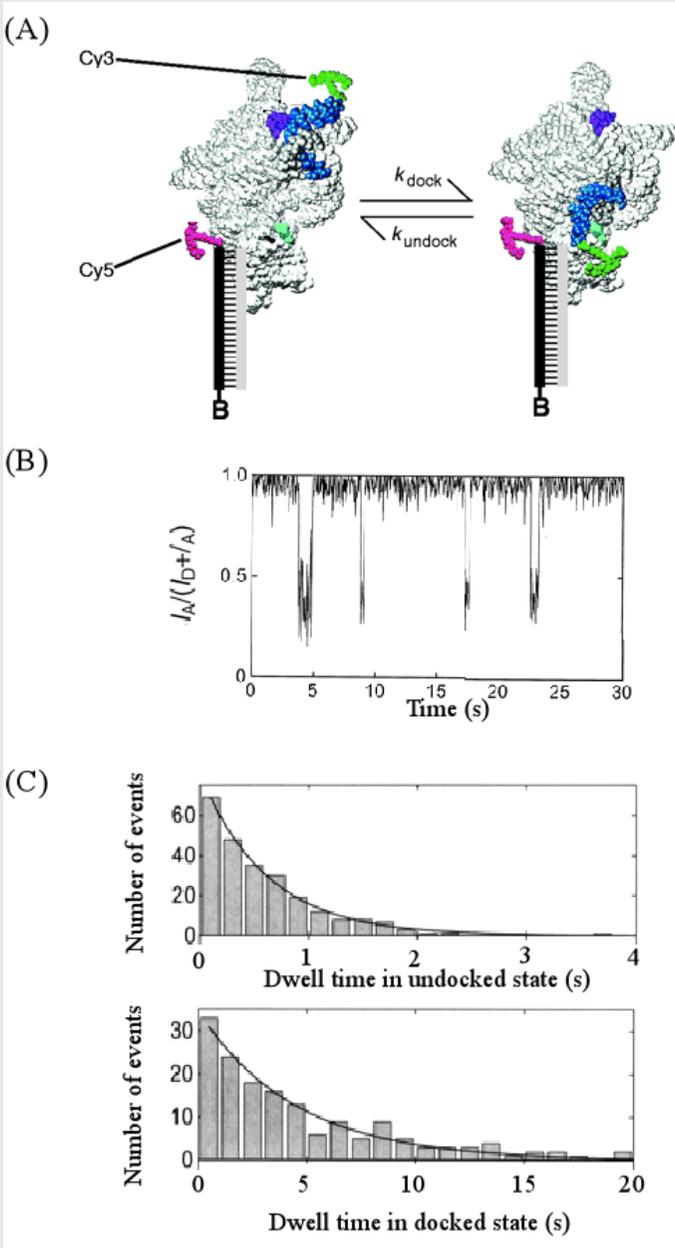
Chemists are also interested in developing reactions that produce new asymmetric centers within molecules. There is significant interest in the development of new catalysts that produce centers of asymmetry, or handedness, within molecules that have no preferred handedness to start. Simple chiral molecules generated by these asymmetric catalysts are important building blocks for new medicines and research tools.

## Seeing Chemistry in Motion

Chemical processes happen over a range of time scales that challenges our comprehension. Some chemical reactions, such as the change of diamond to graphite under normal conditions of temperature and pressure or the spontaneous conversion of left-handed to right-handed amino acids, are so slow that their rate of change is measured in millions of human lifetimes or longer. Contrast these processes with the direct breaking of a chemical bond when a molecule absorbs light. Such a photodissociation process is so fast that it typically takes 10 to 100 femtoseconds (i.e., between  $10 \times 10^{-15}$  and  $100 \times 10^{-15}$  seconds); this is the time required for light to travel about 3 to 30 microns). As the 20th century came to a close, chemical scientists were delighted that they possessed the tools to make kinetic measurements over the full range of reaction rates.

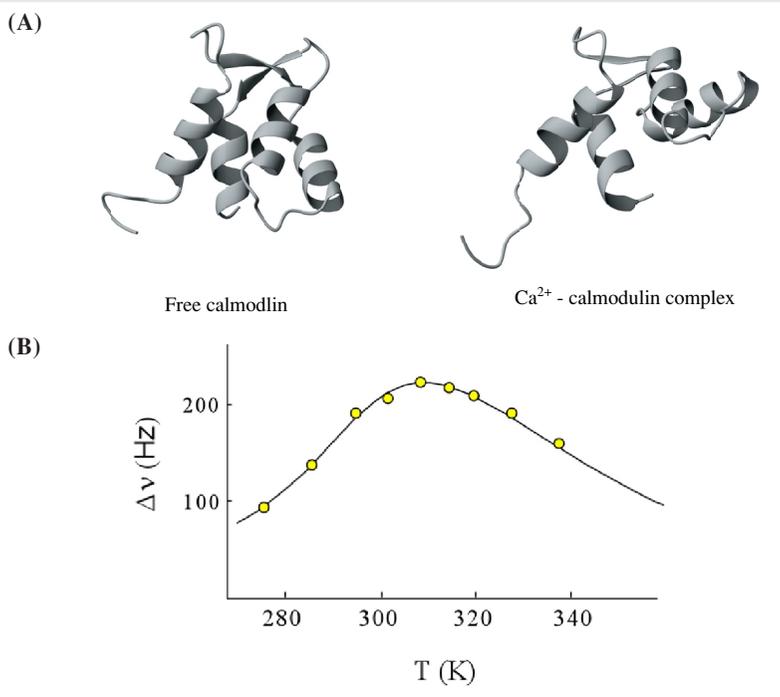
Different changes take place on widely different time scales; consequently, the complex nature of chemical transformations often can be separated into a set of discrete steps. Each step that takes place on a different time scale requires the use of different experimental tools to study it. For example, consider the conformational change and folding of RNA, a key molecule transferring genetic instructions from DNA to build proteins, and a molecule that itself carries out biological transformations. For these molecules conformational changes occur on the time scale of a few seconds. This information has been readily obtained by studying fluorescence resonance energy transfer (FRET) of a single RNA molecule tagged with fluorescent dyes. The energy transfer is a sensitive function of distance between energy donor and acceptor in the molecule. Therefore, by labeling two sites of the RNA by donor and acceptor molecules, it is possible to follow the RNA conformation as a function of time.

(A) Conformational change of RNA illustrating motion of the P1 duplex in the Tetrahymena Group I ribozyme. Cy3 dye attached onto P1, and Cy5 attached on the other end of RNA acts as donor and acceptor, respectively. FRET between Cy3 and Cy5 signals conformational change occurring in RNA molecule. (B) FRET time traces from single ribozyme molecules showing P1 docking and undocking. FRET is defined as  $IA/(ID + IA)$ , where IA and ID are the fluorescence signals from acceptor and donor, respectively. (C) Histograms of the dwell times in the undocked (top) and docked states (bottom) obtained from the FRET time trajectories. The solid lines are single exponential fits of the data giving rate constants for docking ( $k_{\text{dock}} = 1.62 \pm 0.08 \text{ s}^{-1}$ ) and undocking ( $k_{\text{undock}} = 0.224 \pm 0.015 \text{ s}^{-1}$ ), respectively. Reprinted with permission from X. Zhuang, L. E. Bartley, H. P. Babcock, R. Russell, T. Ha, D. Herschlag, S. Chu, *Science*, 288, 2048 (2000). Copyright 2000, American Association for the Advancement of Science.



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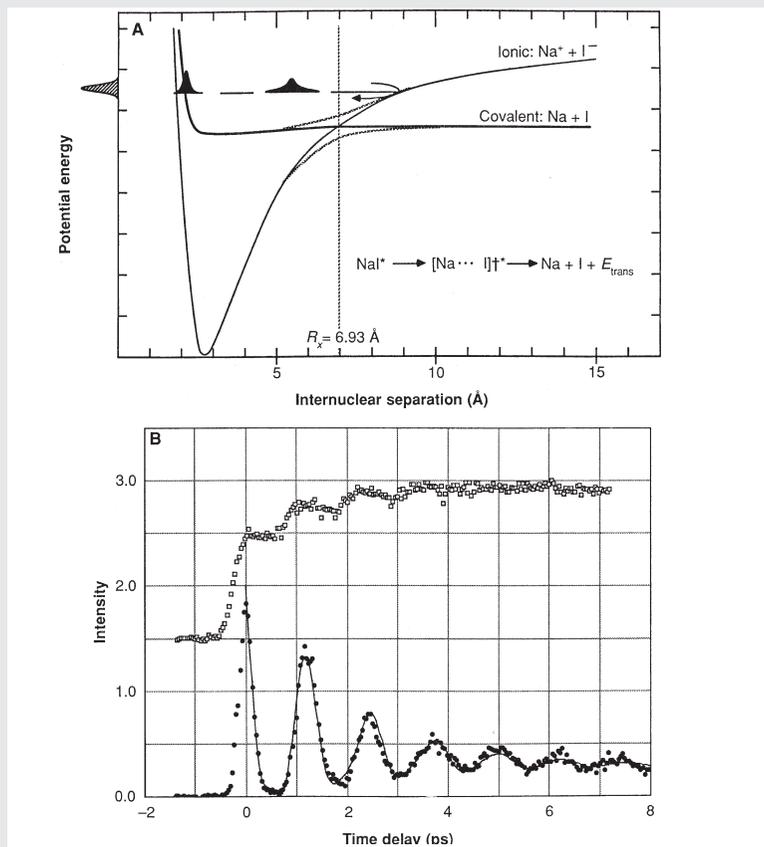
The binding of calcium ion to calmodulin, a major biochemical regulator of ion pumps and receptors, occurs on a time scale about a thousand times shorter than that observed for RNA conformational change. This  $\text{Ca}^{2+}$ -calmodulin binding, which can be followed successfully by nuclear magnetic resonance (NMR), occurs in about ten milliseconds.



(A) Structures of calmodulin with and without  $\text{Ca}^{2+}$  ion binding. Courtesy of Mikael Akke, Lund University, Sweden. (B) Linewidths of  $^{43}\text{Ca}$ -NMR spectrum of  $\text{Ca}^{2+}$ /calmodulin mixture as a function of temperature (circles), together with best fit to the kinetics (solid line). By analyzing the temperature dependence, the activation barrier is determined. Adapted from T. Drakenberg, S. Forsén, H. Lilja, J. Mag. Res. 53, 412 (1983). Reprinted from *Journal of Magnetic Resonance*, 53, T. Drakenberg et al.,  $^{43}\text{Ca}$  NMR Studies of Calcium Binding to Proteins: Interpretation of Experimental Data by Bandshape Analysis, 412-422, (1983), with permission from Elsevier Science.

Other chemical changes can be much faster than the RNA conformational changes illustrated here. Photodissociation of sodium iodide (NaI) in the gas phase occurs on the time scale of a few picoseconds ( $10^{-12}$  seconds). To measure this phenomenon, NaI molecules are irradiated by a sub-picosecond ultraviolet pulse of radiation, and the subsequent events are clocked by another short light pulse that detects the newborn

sodium atoms. The illustrations show the time evolution of the Na-atom wave function.



(A) Potential energy curves for the excited states of sodium iodide showing the crossing of the ground state with the excited state (B) Time evolution of free (empty squares), and bound (filled circles) Na fragments observed by laser-induced fluorescence. Motion of the NaI wave packet as a fraction of the molecules cross from the ionic ground state to the covalent repulsive excited state causes oscillations in the observed signals. Reprinted with permission from A. H. Zewail, *Science*, 242, 1645 (1988). Copyright 1988 American Association for the Advancement of Science.

These examples illustrate only a small part of the range of time scales that chemists and chemical engineers examine in their studies of chemical phenomena. By visualizing chemical transformations, chemical scientists obtain a deeper fundamental understanding of how chemical reactions occur and even develop the ability to create favorable conditions to control some of these reactions.

Usually we talk about reactions in solution, but recently techniques have been developed to follow reactions that occur in a vacuum when a stream of reactant A and a stream of reactant B cross each other in a defined direction, as with molecular beams. From the direction in which the products are ejected and their energies, much fundamental information can be deduced about the details of the molecular processes. Lasers, which emit light-energy in a highly focused beam, are sometimes used to put energy into one of the reactants in a defined way. Such a technique reveals less about the nature of the transition state than about what is called the dynamics of the process—how molecules collide so as to react, and how the products carry away the energy of the overall reaction. The development and application of such techniques were recognized by a Nobel Prize in 1986 to Dudley Herschbach, Yuan Lee, and John Polanyi.

The interaction between experiment and theory is very important in the field of chemical transformations. In 1981 Kenichi Fukui and Roald Hoffmann received a Nobel Prize for their theoretical work on the electronic basis of reaction mechanisms for a number of important reaction types. Theory has also been influential in guiding experimental work toward demonstrating the mechanisms of one of the simplest classes of reactions, electron transfer (movement of an electron from one place to another). Henry Taube received a Nobel prize in 1983 for his studies of electron transfer in inorganic chemistry, and Rudolf Marcus received a Nobel Prize in 1992 for his theoretical work in this area. The state of development of chemical reaction theory is now sufficiently advanced that it can begin to guide the invention of new transformations by synthetic chemists.

Particular interest in recent times has centered on trying to understand the chemical mechanisms by which various biological processes occur. Such complex events as the cleavage of RNA by the enzyme ribonuclease, the multi-step synthesis of ATP *in vivo* (Paul Boyer and John E. Walker received Nobel prizes in 1997 for working this out), and the activity of molecular motors that power bacterial flagellae are now understood in molecular detail. George Wald received a Nobel Prize in 1967 for discovering the chemical mechanism in the eye by which light is transformed into a signal to the brain that produces vision. The recent sequencing of the human genome has provided a molecular foundation from which other complex biological processes might be tackled at a molecular level.

The basic science of chemical reactions has been put to good use for more than half a century in the fuels, plastics, environmental, and biotechnology fields. One story illustrates well the societal benefit of learning to guide the pathways of chemical reactions, in this case via catalysis and process design. The 1997 Draper Prize of the National Academy of Engineering, the engineering profession's highest honor, went to Vladimir Haensel for his 1947 invention of platinum-catalyzed reforming of petroleum. The prize citation explains how, while working for Universal Oil Products Co. (now called UOP), Haensel sought to improve the process by which gasoline was produced from crude oil; thermal cracking of petro-

leum over a clay catalyst yielded only modest amounts of very low-octane gasoline. Haensel proposed using platinum as a catalyst for the refining process, despite the challenges posed by the expense and availability of platinum. He developed a simple method that was efficient in producing more gasoline from the same amount of petroleum and that also produced a remarkably higher-grade fuel. Platinum reforming produces vast amounts of aromatic hydrocarbons, the raw materials used in the manufacturing of plastics and synthetic fibers such as polyester. Platinum-catalyzed reforming has reduced U.S. reliance on foreign oil, broadened the world's long-term energy outlook, helped reduce pollution due to combustion, and saved billions of dollars in transportation costs. These are revolutionary effects on energy, transportation, materials production, and our environment.

For examples such as platinum reforming, designing the reactors is as essential for technological success as is detailing the chemistry. The chemical knowledge and new catalysis are embedded in the process, but other factors are necessary as well. These include transporting materials through the process equipment, mass transfer between the fluid and catalyst, controlling pressure and its effects on physical properties and phase behavior, and mixing and separation processes. Advances in these physical aspects of transformation processes have been essential to modern chemical manufacturing. Effective technological implementation requires integrated knowledge and use of chemical and physical transformation fundamentals.

Important physical transformations between states of matter, not necessarily involving chemical reaction, can occur on changes in temperature or pressure or application of external forces or fields. Such phase transitions have been central to quantitative research in chemical sciences, at least since the time of Robert Boyle in the mid-17th century and, in a more modern context, Sadi Carnot, R.J. Clausius, and J. Willard Gibbs in the 19th century. Suitable choices or changes in temperature, pressure, and other controllable properties can produce abrupt changes (first-order transitions) in the state of a substance—for example, boiling or freezing, or formation of systems having two phases coexisting with distinct phase boundaries between them.

Equations of state relate the phase properties to one another and are an essential part of the full, quantitative description of phase transition phenomena. They are expressions that find their ultimate justification in experimental validation rather than in mathematical rigor. Multiparameter equations of state continue to be developed with parameters tuned for particular applications. This type of applied research has been essential to effective design of many reaction and separation processes.

The last several decades have seen the growing scientific importance of phenomena near critical points, those conditions of system properties where two coexisting phases, such as liquid and vapor, become identical. This is exemplified by the 1982 Nobel Prize awarded to Kenneth Wilson for his theoretical studies of

critical phenomena and continuous or second-order phase transitions. Supercritical fluid processing is exploiting knowledge about this domain of phase behavior for new applications in separations, chemical reactions, and materials production. Supercritical carbon dioxide is now used as a solvent in improved, environmentally benign methods for decaffeination of coffee and for dry cleaning (Chapter 9).

Phase behavior in complex fluids such as polymer blends and block copolymers has been a rich area of the chemical sciences. Near-critical and other transitional phenomena are frequently prominent. Since molecular movement in viscous systems such as these is comparatively slow, phase transitions can be studied more easily in time, and manipulated by quenching and other external influences. Processes for controlled growth of ordered materials are often readily influenced by diffusion, a variety of external fields, and the influence of interacting boundaries, or flow.

Flow processes in materials that contain structural elements, such as polymers and suspensions, can influence important physical and chemical transformations. Thinning or thickening of fluids under shear flow, structural rearrangements that affect physical properties, and flow of granular media are just a few examples where flow produces major changes in a chemical product, often permanent and sometimes helpful. Alignment of polymer molecules in fibers and films is essential to produce high strength. For example, ultra-high molecular weight polyethylene fibers, which appear gel-like when produced, are used in bulletproof vests. Arranging the fibers to cross at 0 degree and 90 degree angles causes the material to have excellent protective properties. Paints, coatings, inks, toners, and adhesives often contain particulate additives precisely for the purpose of producing interactions that respond to the imposition of flow. The science of these interactions is advancing rapidly, through theory and experiment. Extending molecular theories to the length scales of particles has produced detailed descriptions of the behavior of hard spheres, polymer-coated particles, and associating colloids. Experimental insight has come from rheology (the study of the changing form and flow of matter), light scattering, and microscopy, often using national facilities for synchrotron x-rays and neutrons. Frequently systems can be observed under flow to illuminate the "transition states" of these physical transformations.

The importance of physical transformations in making chemical products implies a vast opportunity for understanding structures of many kinds of important chemical products at higher levels and longer length-scales than those of individual molecules. Structured chemical products will be a rapidly growing area, particularly with the investments of financial and intellectual resources that are currently being made in nanoscale science and engineering. In the past 15 years we have seen an accelerating explosion in the ability to formulate, characterize, and predict phase behavior and the resulting transport processes for colloids, surfactant solutions, and block copolymers in particular. Control over syn-

thesis and interparticle forces has allowed selective addition of nonadsorbing, associative, and diblock copolymers, and external electric and magnetic fields have been used to control equilibrium phase behavior and rheology.

Chemists have synthesized a spectacular array of submicron- and nano-particles with well-defined size and atomic structure and very special properties. Examples include CdSe quantum dots and novel spheres and rods. Transport enters the picture via fundamental studies of the physical processes that affect the synthesis, which must be understood for even modest scale-up from the milligram level. Likewise, processes for assembling fascinating face-centered-cubic crystals or ordered multilayers must concentrate on organizing the particles via flow, diffusion, or action of external fields. Near-perfection is possible but requires careful understanding and control of the forces and the rates.

Block copolymers consist of two or more sections of polymer, of which each section is made of a single type of monomer. Block copolymers are representative of a class of structured chemical products where physical chemistry and synthetic chemistry must go hand in hand to create the desired product. The vast effort invested in copolymer microphase separation has recently spawned a number of novel efforts. Studies of the relationship between molecular architecture, ordered-phase morphology, and mechanical properties have shown that multi-block copolymers offer special advantages in product properties that result from the molecular connectivity over the multiple domains that they create. Equally important to mechanical properties are the new transport properties and membrane separation capabilities that structured, composite chemical products can deliver. Another example is the development of block copolymer nanolithography. Ordered monolayers with spherical or cylindrical morphologies are cast, and the minority phase is then removed to permit etching or deposition through the gaps in the remaining continuous phase. The results are holes or posts with lattice spacings on the order of 10 nm over remarkably large areas. In both these examples, transport processes limit the rate of annealing due to thermal motion, but when driven by flow or external fields, may conspire to provide even longer-range order. Application of external fields in physical transformations produces effects analogous to those of catalysis in chemical reactions—enhancing the rates and selecting the products. Transport phenomena play crucial roles in both the creation and performance of structured chemical products. This idea has little parallel in mechanistic studies of reactions to synthesize simpler molecular chemical products.

Transport phenomena present an important challenge in the progression toward smaller length-scales of microscale, nanoscale, and molecular scale. Chemical processing will need to exploit small-scale reactors in new applications. Understanding chemical and physical transformations at these length-scales will be necessary for advances in microfluidics, for progress in developing new chemical and biological sensor applications, and for realizing the promise of self-assembly as a chemical processing method. Molecular models of structured fluids (poly-

mers, suspensions, composites), validated in part by single-molecule mechanical measurements, will be crucial to the growth in this area.

### CHALLENGES AND OPPORTUNITIES FOR THE FUTURE

How can we obtain direct information on the molecular details of a reaction path and harness this for the design of new processes? While femtosecond spectroscopy has made it possible to observe reactions on a short time scale, a major challenge is to devise ultrafast techniques, such as superfast electron diffraction, that will permit observation of the actual molecular structure of a transition state, not just its rate of passage. As a general goal, we want to be able to make moving pictures of the reactions themselves, observing all the intermediate states and the rates at which they interconvert. Such moving pictures can be generated even now, by computer simulation of the reaction; the problem is to determine whether those pictures are correct. Thus a second challenge is to interface with theoretical chemistry in getting the best possible calculations, and then devise experimental tests of the major theoretical predictions to see whether experiments confirm the correctness of the calculations.

Most mechanistic work has focused on chemical reactions in solution or extremely simple processes in the gas phase. There is increasing interest in reactions in solids or on solid surfaces, such as the surfaces of solid catalysts in contact with reacting gases. Some such catalysts act inside pores of defined size, such as those in zeolites. In these cases only certain molecules can penetrate the pores to get to the reactive surface, and they are held in defined positions when they react. In fact, the Mobil process for converting methanol to gasoline depends on zeolite-catalyzed reactions.

There is also increasing interest in reactions involving organometallic compounds, at the interface between organic and inorganic chemistry. Many such reactions are useful in synthesis, where the organometallic reagents can have important properties as catalysts. Many details of reaction mechanisms in organometallic chemistry are yet unclear; understanding these mechanisms will allow the development of improved catalysts.

Much work has been done to help understand how metal ions react or catalyze reactions in solution. Many enzymes also use bound metal ions to catalyze their reactions, and there is still need to understand how they work. When we do understand them in detail, we should be able to produce biomimetic catalysts for useful processes in manufacturing.

When molecules react thermally, at room temperature or on heating, they are in their lowest electronic states. However, when reactions occur on irradiation of the molecules with visible or ultraviolet light, the processes involve species in electronic excited states. Some of the details of such processes are known, but there is still much to do. Since photoexcitation is important in many areas—photosynthesis, photography, electronic displays, solar cells, cancer-causing ul-

traviolet interactions with the skin, identification of interstellar molecules, degradation of materials and dyes by sunlight—it is important to investigate these processes. As part of understanding the chemical universe with all the substances and transformations that are possible, or at least learning their major features, basic chemical science needs to understand transformations of excited states, not just of ground states.

The design of multicomponent processes remains an important challenge. Conventional process development has focused on single reactions and their optimization. New processes that involve reaction cascades, where the product of one reaction feeds the next, will permit more efficient production of industrial or biomedical products. A detailed understanding of biological metabolic networks will facilitate the design of similarly complex artificial systems. Computational analysis of such interconnected reaction networks will be important for reaction modeling and design.

It is a continuing challenge to understand the properties of enzymes. They are usually very effective catalysts, able to speed up reactions of many biological substances in both the forward and reverse directions. Also, their activities can be modified by inhibitors that bind to them, and many medicines such as cholesterol-reducing drugs function as enzyme inhibitors. To some extent the details of the catalytic mechanisms of enzymes have been elucidated, or at least guessed at. However, there is not yet a real understanding of the factors that contribute to enzymes' high effectiveness, and we do not yet have good examples of synthetic analogs of enzymes that catalyze the same reactions with the same or better speeds and selectivities. A full understanding of enzymes will enable the introduction of synthetic catalysts, which will be of great value in manufacturing. The introduction of synthetic catalysts may also contribute to the development of a new class of medicines. Medicines today operate mainly by binding to various biological molecules, but they don't carry out catalyzed reactions in the body. If we fully understand enzymes well enough to be able to make new catalysts of similar effectiveness, such artificial enzymes could be an exciting class of molecular machines and medicines. They could destroy undesirable species or toxins, or promote the formation of materials that are present in insufficient quantities due to some diseases. We are also learning how to recreate the process of evolution through natural selection in a test tube.<sup>1</sup> New enzymes can be evolved by applying selective pressure for improved properties or even for totally different functions.

By manipulating genes, chemists have learned to create new enzymes with new functions. To do this rationally and predictably, it is critical to understand the structures and mechanisms of the genes that are being modified. Enzymes and other biological components often function in clusters, in multicomponent sys-

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<sup>1</sup>A. D. Keefe and J. W. Szostak. *Nature* 410 (6829) 715-718, 5 Apr 2001.

tems. Thus even when we understand fully the chemical properties of a pure enzyme, a challenge remains—to understand the properties of interacting molecules, including enzymes, assembled into well-defined structures.

### WHY ALL THIS IS IMPORTANT

Any list of applications such as the examples presented in this chapter is always too limited. It is more realistic to say that there are still big gaps in our understanding of the molecular details of chemical and biochemical reactions. The chemical universe is filled with transformations, both natural and invented. We apply them in manufacturing, we admire them in biological chemistry, but we do not yet know enough about their details. With understanding, when we have it, will come greatly improved methods for synthesis and manufacturing. Increased understanding of the details and special character of transformations will also lead to applications not yet even thought of, as has happened with every big advance in scientific understanding.

## Isolating, Identifying, Imaging, and Measuring Substances and Structures

### **Some Challenges for Chemists and Chemical Engineers**

- Improve the tools for imaging and determining structure so that detailed chemical structures can be determined with tiny amounts of non-crystalline material.
- Improve the ability of instruments to detect and quantify very low concentrations of important substances, even in very small volumes.
- Develop effective methods for detecting dangerous materials, even when they are hidden.
- Understand the chemistry that occurs in interplanetary and interstellar space, for which spectroscopy is the primary tool available.
- Develop instruments for on-line process control that bring the power of modern analytical and structure-determination methods to chemical manufacturing technology

### **GOALS**

Chemical scientists want to explore the natural world and identify all its chemical components. They also want and need to identify all of the new chemical substances produced directly and indirectly as a result of their synthetic and

manufacturing endeavors. As described in Chapter 7, much of this has involved learning the nature of the substances that are part of, and produced by, living organisms. Generally it is necessary to learn how to separate complex mixtures into their pure components, and then determine the molecular structure of each component. This sequence is also necessary for the substances that are created in the laboratory or in manufacturing. If a mixture is produced, it must be separated into its components, and each new species must have its chemical structure determined.

Detecting known substances, and determining their quantity, is also important. In synthetic research, it is essential to know the relative proportions of various reaction products. In manufacturing, it is important to detect any impurities in the product and to determine whether they are present in a significant amount. Analytical characterization is critical in pharmaceutical products, for instance. Products for practical uses—paint or adhesives, for example—will typically consist of several components. For proper and reliable performance it is important to measure the amounts of each of the components as part of a manufacturing quality control system. Manufacturers also commonly need to analyze the raw materials they receive, measuring the amounts of various substances in them to be sure that the material meets their requirements. Before it can be correctly processed into steel, iron ore must be analyzed to determine how much of other components need to be added to produce a metal alloy of the desired composition and properties.

The determination of quantity in complex mixtures is also vital in health care and medicine. We are all familiar with the medical examinations in which a sample of blood or urine is sent to a laboratory for analysis. The procedures used have been developed by chemists, and are performed by trained chemical technicians. The high level of automation achieved by the chemists who designed these analytical procedures has greatly reduced the costs of such analyses. Clinical analysis continues to be driven by a need for better methods to detect and measure important proteins, for example, that while present in tiny amounts are relevant to our health and well-being.

There is a constant need for better methods of chemical analysis, driven by our need to know “What’s in that, how much is present, and how long will it last?” The frontiers in this field lie in improving sensitivity to detect vanishingly small quantities, to separate extremely complex mixtures of chemical substances, and to assess the structures or compositions of components. Measurements using very small or very dilute samples can present a major challenge in clinical medicine or environmental analyses. Moreover, often we must deal with all of the above determinations in extremely small spaces, such as that of a living cell. Fundamentally new approaches may be needed to achieve these objectives. As an important example, there is currently a need for sensitive methods to detect—in a high-throughput environment—explosives in airplane baggage and in land mines in war-torn areas (see also Chapter 11). These problems are being approached by

developing very sensitive arrays of chemical detectors, sometimes called artificial noses, that can detect and identify volatile components of explosives in very small amounts. Other problems are learning to detect chemical and biological warfare agents, both on the battlefield and in civilian areas, and to detect trace components in our environment, either anthropogenic or of natural origin, that offer health risks to living organisms: human, beast, insect, fungus, and plant.

## PROGRESS TO DATE

### Structure Determination

A vital activity of the chemical sciences is the determination of structure. Detailed molecular structure determinations require identifying the spatial locations of all of the atoms in molecules, that is, the atomic distances and bond angles of a species. It is important to realize that the three-dimensional architecture of molecules very much defines their reactivity and function. However, molecules are dynamic, a feature that is not reflected by static pictures. This last point requires further explanation. Because the atoms in all molecules move, even in the limit of the lowest temperatures obtainable, molecular structures really describe the average position about some equilibrium arrangement. In addition, rotations about certain bonds occur freely at common temperatures. Consequently, some molecules exist in more than one structure (conformation). Some molecules are so floppy that structural characterizations really refer to averages among several structures. Yet other molecules are sufficiently rigid that molecular structures can be quite precisely determined.

The techniques available to achieve molecular structure determinations are limited. They include structural analysis with diffraction techniques—such as electron, neutron, and x-ray diffraction—and various absorption and emission techniques of electromagnetic radiation—such as microwave spectroscopy and nuclear magnetic resonance (NMR). For molecules with unpaired spins a companion technique of electron spin resonance spectroscopy (ESR) is highly informative.

A number of other spectroscopies provide information that is related to molecular structure, such as coordination symmetry, electronic splitting, and/or the nature and number of chemical functional groups in the species. This information can be used to develop models for the molecular structure of the system under study, and ultimately to determine the forces acting on the atoms in a molecule for any arbitrary displacement of the nuclei. According to the energy of the particles used for excitation (photons, electrons, neutrons, etc.), different parts of a molecule will interact, and different structural information will be obtained. Depending on the relaxation process, each method has a characteristic time scale over which the structural information is averaged. Especially for NMR, the relaxation rate may often be slower than the rate constant of a reaction under study.

The application of theoretical tools for predicting molecular structure, such as *ab initio* calculations and density functional methods, are discussed in Chapter 6. These tools provide only a first approximation to the molecular structure. There is much room for further development of theoretical molecular structure calculations, but even so such methods have already become a standard part of molecular structure determinations.

The following section presents a variety of instrumental spectroscopic techniques for the determination either of molecular structure or of parameters related to molecular structure. The applicability of each method, its particular advantages as well as its limitations, are presented. It is not an exhaustive list. The spectroscopic methods are discussed in order of increasing excitation energy.

### *Nuclear Magnetic Resonance Spectroscopies*

NMR has proven to be invaluable as a tool for structure determination, particularly of new compounds isolated from nature. All synthetic chemists use NMR to see whether they have made the product they want, even if it is a previously unknown molecule. In fact, NMR has really revolutionized the practice of organic synthesis. NMR is typically applied to molecules in solution, so it can be used with noncrystalline materials, for which x-ray crystallography is not possible. It also can be used to learn whether the structure determined in the solid state by x-ray methods is maintained in solution. This is particularly important for proteins, which are flexible enough that they can change shape to some extent when they dissolve. A Nobel Prize in 1991 went to Richard Ernst for inventing new techniques in NMR that are important tools in the study of proteins. Kurt Wüthrich shared a Nobel Prize in 2002 for developing NMR methodology that enables determination of the three-dimensional structures of biological macromolecules in solution.

NMR finds its main application in the analysis of solutions, using  $^1\text{H}$  as the most sensitive nucleus;  $^{13}\text{C}$ ,  $^{19}\text{F}$ , and  $^{31}\text{P}$  nuclei are also used frequently. NMR yields information on chemical functional groups of organic ligands and has revolutionized work in synthesis. Multi-dimensional techniques can be used for finding spatial connections between nuclei and gaining information on molecular dynamics. An important recent advance is NMR on solids, not solutions, with which it is possible to study the structures of polymers, of proteins in membranes, and of chemicals immobilized on solid supports. The application of NMR to imaging the human body, or magnetic resonance imaging (MRI), has revolutionized the practice of medicine.

The major current limitation of NMR is its sensitivity (ca.  $10^{-4}$  M in  $^1\text{H}$ ,  $^{13}\text{C}$ ,  $^{19}\text{F}$ ,  $^{31}\text{P}$ ). It is expected that higher sensitivities will be reached in the future as more powerful magnets with improved instrumentation and software become available. The ultimate goal would be to perform NMR analyses of single molecules.

### *Rotational Spectroscopies*

Rotational spectra provide measurement of the moments of inertia of a chemical species. Bond angles and bond lengths can be derived by making isotopic substitutions and measuring the resulting changes in the moments of inertia. A major drawback of rotational spectroscopies is the limited information contained in a measurement of the moment of inertia. Consequently, while quite precise, it is generally limited to smaller molecules. It is the chief technique used to identify molecules in outer space, such as the components of interstellar gas clouds.

### *Vibrational Spectroscopies*

Infrared and Raman spectroscopies provide complementary information concerning the type of functional groups present, as well as bond strengths in a molecule. Recent experiments using infrared pulse sequences offer the tantalizing possibility of bringing to infrared and Raman spectroscopies the same advantages that have been realized in pulsed NMR spectroscopies—greater sensitivity and higher information content. A major limitation of vibrational spectroscopies has been the congestion of overlapping features at lower frequencies. However this congestion makes an infrared spectrum a literal fingerprint of the structure of small molecules, so the identity of known molecules can be assessed from a library of their spectra. Some of the molecules in interstellar space have been identified by their infrared spectra. New resonant enhancement techniques can provide useful information about molecules on surfaces and at interfaces.

### *Electronic Spectroscopies*

The interaction of species with shorter wavelengths of radiation causes electronic excitation (bound-bound electronic spectroscopy) or even ejection (bound-continuum photoionization). These events also show the fine structure of the motions of the nuclei. In addition, nuclear motions moderate the energies of the ejected electrons, and an analysis of the electron energy provides additional chemical information. Thus, x-ray photoelectron spectroscopy (XPS) is an excellent technique for determining an atom's electron binding energies, at least for species on the surface of the material under study. Valuable information about surfaces can also be obtained from ultraviolet photoelectron spectroscopy (UPS), a technique that reveals ionization potentials and molecular orbital orderings for substances in general.

By comparing the chemical shifts and peak heights of an unknown with standards or known reference materials, some predictions of the unknown structure can be made. In some exceptional but important cases, such as the photodetachment of negative ions, the wavelength of light causing photoionization is in the visible or even the near infrared, allowing extremely precise structure determinations.

Another noteworthy example is x-ray absorption fine structure (EXAFS). EXAFS data contain information on such parameters as coordination number, bond distances, and mean-square displacements for atoms that comprise the first few coordination spheres surrounding an absorbing element of interest. This information is extracted from the EXAFS oscillations, previously isolated from the background and atomic portion of the absorption, using nonlinear least-square fit procedures. It is important in such analyses to compare metrical parameters obtained from experiments on model or reference compounds to those for samples of unknown structure, in order to avoid ambiguity in the interpretation of results and to establish error limits.

The absorption spectra in the x-ray absorption near edge structure (XANES) region contain information concerning coordination geometry and metal ion valence. EXAFS and XANES data can be obtained on samples in different physical states or in solution and can be made element selective by tuning the wavelength used for the study. A drawback of these absorption spectroscopies is the need to bring the sample to a large dedicated facility.

### *Nuclear Structure Spectroscopies*

Nuclei also have bound energy levels that can be accessed with gamma-ray sources. Of great chemical interest is Mössbauer spectroscopy, which takes advantage of the recoil-free emission of gamma radiation from a solid radioactive material. Because the gamma emission is recoil-free, it can be resonantly absorbed by stationary nuclei in a solid. Typically, the gamma ray source is mechanically vibrated back and forth to Doppler shift the energy of the emitted gamma radiation. A detector records the frequencies of gamma radiation that are absorbed by the sample as the energy of the gamma radiation is scanned by Doppler shifting.

The nuclear transitions are very sensitive to the local environment of the atom, and Mössbauer spectroscopy is a sensitive probe of the different environments an atom occupies in a solid material. By analyzing the chemical shifts and quadrupole splitting in Mössbauer spectra of samples containing Mössbauer-active nuclei, information on the state of oxidation and the local structure can be obtained. Only a few nuclei can be used for this purpose, so this method has limited but powerful applications.

### *Diffraction Techniques*

X-ray, neutron, and electron diffraction techniques are used to determine crystal structures and can thus be used for molecular structure determinations. Because of its high resolution and applicability to small and often weakly diffracting samples, x-ray crystallography and powder diffraction are by far the methods of choice for most structure determinations on crystalline compounds,

either single crystals or crystalline powders. Diffraction techniques are not applicable to amorphous phases at present, but the exciting possibility looms on the horizon to use ultra-fast techniques to obtain diffraction patterns of possibly as little as one biological molecule (see below).

The intensity and tunability of synchrotron radiation have revolutionized the application of x-rays for studying the structure of macromolecules, enabling much higher resolution information to be obtained on increasingly large and complex molecular systems. The average bulk crystalline structure determined from diffraction studies is expressed as simple, small, symmetric arrangements of atoms in a unit cell. However, local deviations from this average structure are often the driving force behind the collective behavior of a crystalline compound. Neutron crystallography has the unique advantage of high contrast for the location of hydrogen atoms, so it affords information complementary to that normally obtained from x-ray crystallography.

As conventionally applied today, x-ray methods give rise to “time-averaged” structural information. Since many chemical processes, including the making and breaking of chemical bonds, occur in the subpicosecond time domain, time-resolved structural information has been limited and only indirectly available. Recent developments in electron diffraction and soon-to-be-available x-ray laser sources could dramatically improve the investigation of structural dynamics. Compressed electron pulses can be produced with reasonable intensities and widths of a few picoseconds; these are being used to study relatively simple molecular reactions. X-ray free-electron lasers, based on using high energy linear accelerators providing beams to long undulators, have the promise of easily reaching pulse lengths of only a few hundred femtoseconds and, with additional magnetic and optical compression schemes, likely the regime of only a few femtoseconds. Such x-ray free-electron lasers might have sufficient photons in a single pulse to record an entire diffraction pattern, hence bringing the most powerful tools used today for structural determination to bear on understanding chemical and biological reactions.

A major limitation of diffraction techniques has been the need to obtain crystalline samples. If scientists could learn how to crystallize large molecules in a routine manner, a breakthrough would result. In the biological area, this limitation is keenly experienced for membrane-bound proteins, which are important in many biological functions. Scientists are now devising techniques and strategies to crystallize these proteins—if not in three-dimensional, then in two-dimensional lattices.

Future development of spectroscopic structure-determination methods will depend on the availability of more powerful photon and particle sources as well as advances in photon and particle detectors. Impressive progress has been made in molecular structure determinations based on advances in computation power and in computational algorithms, such as fast Fourier-transform techniques, for nearly every form of spectroscopy and diffraction analysis. Hajdu and co-work-

ers<sup>1</sup> have presented calculations estimating radiation damage of samples. They suggest that useful structural information might be obtained before radiation damage destroys the sample by using femtosecond x-ray pulses. Moreover, their calculations indicate that sufficiently bright light sources might be capable of imaging ultrasmall samples at sizes approaching that of a single biological molecule.

Structure determination has greatly advanced with the invention of new ways to use x-ray crystallography, mainly new mathematical methods that permit the interpretation of the observed patterns of diffraction of x-rays by a crystal, translating it into the molecular structures in the crystal. A Nobel Prize in 1985 to Herbert Hauptmann and Jerome Karle recognized such an advance.

### *Mass Spectrometry*

The “weighing” of a molecule of a chemical substance and of its fragments has great utility in both assessing molecular identity and determining molecular structure. The determination of molecular weight is after all one of the most elemental aspects of puzzling out the structure and identity of an unknown sample or a new substance. Furthermore, if the molecular mass can be determined with sufficient accuracy, the elemental formula of the substance can be estimated or at least the possible choices narrowed considerably. For materials such as those encountered in biologically derived samples, where the quantities available are very small, determining a molecular weight and elemental formula are extremely important steps. Ion cyclotron resonance mass spectrometry (ICR-MS) has been especially effective at exact mass determinations.

Mass spectrometry requires that the material being studied be converted into a vapor. Great strides have been taken in recent years to address this problem, especially in enticing large, thermally fragile (bio)molecules into the vapor state. Matrix assisted laser ionization-desorption (MALDI) and electrospray ionization (ESI) are two current forefront methods that accomplish this task. Even components of bacteria and intact viruses are being examined with these approaches. John B. Fenn and Koichi Tanaka shared in the award of a Nobel Prize in 2002 for their respective contributions to development of electrospray ionization and soft laser desorption.

A decade or so ago, mass spectrometry was regarded as a “mature” area of methodology. The invention of new ways to volatilize molecules, from solids and from surfaces, has revolutionized and re-invigorated this field. It is an excellent example of how new ideas can make even supposedly “dead” areas find new life.

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<sup>1</sup>Neutze, R.; Wouts, R.; Van der Spoel, D.; Weckert, E.; Hajdu, J. *Nature*, 406 (6797) p. 752, 2000.

## Measurement Science, or Analytical Chemistry

The scope of this branch of chemistry encompasses both the fundamental understanding of how to measure properties and amounts of chemicals, and the practical understanding of how to implement such measurements, including the design of the necessary instruments. The need for analytical measurements arises in all research disciplines, industrial sectors, and human activities that entail the need to know not only the identities and amounts of chemical components in a mixture, but also how they are distributed in space and time. These sectors of need include research in specific disciplines (such as chemistry, physics, materials science, geology, archeology, medicine, pharmacy, and dentistry) and in interdisciplinary areas (such as forensic, atmospheric, and environmental sciences), as well as the needs of government policy, space exploration, and commerce.

Practical needs for analysis come from the activities of industrial enterprises and government functions that span manufacturing, shipping, communications, domestic power, water supplies, waste disposal, forensic analysis, environmental policies, international verification of quality and quantity (metrology), and far from least of all, national security. The need for measurements of chemicals is ubiquitous—measurements of the mass and dimensions of chemical substances and of their capacity to adsorb heat, to absorb or reflect light, and to respond to pressure and temperature. Many measurements also must be made under varying constraints of speed, cost, and location of the measurement.

This enormous diversity of customers seeking analytical information places pressing and urgent demands on chemical scientists. In response, many great successes have been achieved but, at the same time, fast-moving advances in science, technology, and human activity continue to awaken sleeping giants that demand new, better, faster, cheaper, more sensitive, and more selective measurements.

The following is an outline of some success stories in analytical measurements. They are categorized in terms of progress in improving sensitivity for measuring very small quantities, of dealing with sample complexity, of measuring large molecules, of making measurements in small dimensions, and of increasing the throughput of new analytical information.

### *Sensitivity*

Nearly every area of measurement science can boast of progress in measuring ever-smaller quantities of chemicals, but several stand out in their stunning trace-analysis capabilities. Trace-metal analysis has come to be dominated by methods that volatilize the sample and then either measure its spectroscopic emission or absorption, or measure the masses of the gaseous metal ions using mass spectrometry. Volatilization is accomplished by various thermal means that include flames, furnaces, and inductively coupled or microwave plasmas. The com-

bination of the inductively coupled plasma with mass spectrometry allows high-sensitivity analysis of virtually every metallic element in the periodic table. These methods are used world-wide for trace-metal analysis.

Lasers have innumerable uses in measurement science; in the excitation of molecular emission (fluorescence) they have become workhorses of analytical instruments and have produced remarkable levels of analytical sensitivity. Lasers are widespread as components of detectors in commercialized chromatographic instruments and clinical analyses. Laser-induced fluorescence has been carried to the ultimate sensitivity of detecting single molecules—there is no more sensitive measurement than this! The very idea of measuring ultralow concentrations loses its meaning when one detects a single molecule, but the fruit of this remarkable accomplishment is that one can contemplate measuring variations in properties of individual molecules, including enzymes and other proteins. In addition, by following the time behavior of a single molecule it would be possible to unmask many important aspects of structure, kinetics, and function of molecules that are hidden by measurements over averages of many molecules. This sensitivity advance revolutionizes how chemical scientists think about measuring molecular behavior, which in the past has always reflected averages of many molecules. Single-molecule spectroscopy thus offers valuable information that cannot be obtained by studying a bulk sample.

In clinical analysis, one of the recent advances has been the use of antibodies to detect biologically important substances, including medicines. Chemists and chemical engineers devised ways to translate the binding of a molecule to an antibody into a detectable signal, sometimes amplifying the signal by an enzyme-catalyzed reaction that could be modulated by antibody binding. Such methods have largely replaced related methods using radioactive tracers.

### *Sample Complexity*

Sample complexity refers to measurements of mixtures of chemicals and to their context. Complexity can mean large numbers of similar chemicals being simultaneously present (petroleum for example), mixtures of very large similar molecules (biomolecular systems), reactivity and thermal fragility of mixture components, and the context of the analysis (such as detection of explosives in airport luggage). The invention of various methods for separating the chemical components of complex mixtures has benefited enormously from the techniques generally known as chromatography and electrophoresis. These techniques and the instruments used in them are constantly being improved.

The principal analytical methods for complex samples are those that separate the mixture by differential migration and then detect the separated components. The separation methods are chromatography, electrophoresis, and field flow fractionation; the detection methods—which need not be selective but must be sensitive—include absorption, laser-induced fluorescence, electrochemistry, and mass

spectrometry. Gas chromatography (GC), high-performance liquid chromatography (HPLC), and capillary electrophoresis (CE) have been extremely successful. HPLC has become the backbone of the pharmaceutical industry, providing essential information on purity (chemical and isomeric) of candidate and manufactured drug agents. GC is routinely the method of choice for gaseous or easily volatilized mixtures, and is commonly used with a mass spectrometer to identify the mixture components as well as to detect and measure their quantities. CE is the most powerful existing separations method (by orders of magnitude), and it is used for very difficult separations. As analytical chemistry has advanced into the world of molecules that biology creates, CE is the method of choice for the hugely complex mixtures of chemicals present in living organisms and their cellular sub-components. CE has been employed for separation of the contents of individual cells and subcellular compartments (organelles), and it is the enabling analytical method for the Human Genome Project. An important frontier continues to be practical ways to combine the merits of different separation methods, such as HPLC-CE, to create hybrid separation techniques.

Other analytical approaches to complex systems include methods that respond selectively to individual chemicals (or a selected class), the detection of which is of paramount importance. Examples are chemical and biological warfare agents, industrial pollutants and toxins, and carbon monoxide in the air in our homes. Attaining analytical selectivity outside a pristine laboratory setting is one of the most difficult and widely unsolved analytical needs. Ion mobility spectrometry (IMS) and gas chromatography/mass spectrometry (GC/MS) are on trial in airport security checkpoints. While one can point to many successes, including the CO detector in your home, analytical chemistry continues to struggle for sensitivity and selectivity in competition with nose-based odor detection by dogs!

### *Macromolecules and Biomacromolecules*

The birth of polymer science provoked numerous new analytical challenges several decades ago; the existing thrust of chemical sciences into molecular biology is now provoking many more challenges at a rapid pace. Polymers, along with pharmaceuticals, are arguably the most important and beneficial substances that synthetic chemistry has brought to the human race. Synthetic polymers generally consist of individual molecules having different chain lengths and molecular weights. This complexity is an important factor in determining properties of the polymer. Understanding of relations between polymer structure and properties has been aided enormously by the development of gel permeation chromatography (which measures the dispersity of polymer chain length), of infrared spectroscopy (which measures functional groups), and of thermal methods like differential scanning calorimetry (which detects polymer crystallinity).

There have likewise been early successes in addressing measurements of biopolymers, particularly their molecular weights, and to a more limited extent

their structure and folding. The most important techniques for structure determination, in addition to x-ray crystallography, include high-field nuclear magnetic resonance (NMR) spectroscopy and mass spectrometry (MS). A host of computer-reliant nuclear relaxation protocols and high-field magnet technology have combined to cement an NMR foundation that has brought about a 30-fold advance in terms of chemical shift resolution from the first commercial introduction of NMR in the 1960s. In mass spectrometry, there is an ongoing evolution of ways to entice large, thermally fragile biomolecules into the gas phase; the methods of electrospray ionization (ESI) and matrix-induced laser desorption-ionization (MALDI) are presently the most widely adopted.

### *Small Dimensions*

The measurement of a chemical on a surface or in a small volume has historically been quite challenging. The amounts of sample are small, so the measurement must be sensitive; the sample is spatially localized, so the measurement must be spatially selective; and the sample may exhibit ordering that the measurement must be able to detect. The advances in measurement capabilities in this arena have been truly remarkable and are ongoing. Most of the measurements are based on principles that were unknown 50 years ago. Surface analysis can now call on x-ray and Auger photoelectron spectroscopy (AES) to measure emitted photoelectrons, revealing the identity of atoms within several nanometers of a solid surface. Secondary ion mass spectrometry (SIMS) measures the emitted-ion consequences of crashing energetic or heavy ions onto the surface. Molecular ordering and quantities on surfaces can be delineated using vibrational spectroscopy, surface plasmon resonance spectroscopy, and Raman and surface enhanced Raman spectroscopy (SERS), all of which have been enabled by the laser. These advances in surface composition and structure analysis have been crucial in the development of the microelectronics industry, which lives or dies by the properties and composition of surfaces.

Imaging of the lateral composition and topography of surfaces has long been an important area and includes topics like electron microscopy—which has made phenomenal advances in recent years—and scanning Auger electron spectroscopy. The measurement of ordering and arrangements of atoms and molecules in a small volume or on a surface was given a quantum leap by the invention of scanning tunneling microscopy (STM) and its progeny of various atomic force and surface force microscopies. The enabling tools in the new instruments were (again) the laser, piezoelectric materials, and computer instrument-control. It is presently possible to visualize the ordering of atoms on a surface, and even to arrange individual atoms, such as “quantum corrals,”<sup>2</sup> with the contacting tip-

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<sup>2</sup>S. L. Silva and F. M. Leibsle, *Surface Science*, 441, L904, 1999.

probe. Much further understanding of the structures of semiconductor surfaces has been derived from STM measurements, with important technological dividends. DNA chains lying on a surface can be imaged, and even individual molecules can be stretched in order to understand the energy of their folding. Imaging of molecularly soft surfaces such as the surfaces of cells offers an enormous potential for understanding organization of molecules in natural life systems. The probe tips of surface probe microscopies can also be made chemically sensitive. This is an exciting development by giving us a new dimension of molecule-scale imaging of chemical properties, for instance by detecting interactions between a molecule on a probe tip with a receptor site on a surface. Emerging research on nanostructures will rely heavily on microscopy, including its STM and surface forces forms.

There have also been major advances in measuring transfers of electrons within small sample dimensions. The science of attaching chemicals to electrodes (chemically modified electrodes) has enabled measurements of electron transfer kinetics associated with electrocatalysis and electroanalysis. Significant applications include attaching enzymes to the electrode coatings for use in, for example, the monitoring of blood glucose for diabetics. Another small-dimension analysis is enabled by using microscopically small electrodes, which are capable of detecting, in real time, the single-vesicle release of neurotransmitters from neuronal cells. These microelectrodes are having a substantial impact on the general science of neurochemistry. Overall analysis in small dimensions seems to be in an enormously promising infancy, and is far from having achieved its limits even with existing ideas.

### *Throughput of Analytical Information*

The worlds of science and technology continually demand more information per unit time (and per unit cost); there is an ongoing revolution in response to this demand. The Human Genome Project, for example, provoked advances in capillary electrophoresis instrumentation that can now produce sequencing results on the order of one base pair per second. Combinatorial synthesis has precipitated orders-of-magnitude increases in the demand for the analysis of structural and reactivity information. In both DNA sequencing and combinatorial chemistry, the concept of “parallel” analysis has emerged, in which instrument design focuses on simultaneous analysis of many different samples. The scope of parallel analysis can be expected to grow for years to come. A significant concept in this emerging field is miniaturization of the entire measurement into a “Star Trek”-like microchip device that would allow instant analysis of a microsample with a microinstrument. The true capabilities of miniaturized instruments remain to be defined, but they are already impressive. Chip technologies hold the promise of allowing many parallel measurements to be done simultaneously at little cost.

### *Process Analysis*

Monitoring the course of chemical transformations during chemical processing and manufacturing is a crucial component of commercial activity. Desirably the analysis is in real time and with the required selectivity and sensitivity to adequately inform the process engineer.

A possible future process analysis challenge is monitoring a chemical self-assembly process, where chemists and chemical engineers want to know about the “extent of reaction.” The chemical process may involve covalent chemical transformations, or be simply the adoption of the desired physical structure. The tools could be optical (UV-visible or IR absorption, for example) or measurements of density or heat evolution. When the evolution of structure effectively captures the “extent of reaction,” structural characterization tools should be sufficient. More difficult problems would be posed for process control in multicomponent materials with complex structural features where the measurements should be real-time (instantaneous) and provide information for feedback control of the process. The analytical time constants required for real-time measurements would be less than that inherent in the self-assembly, which may have widely varying inherent characteristic times, and are influenced by extensive molecular transport and organization. The close coupling of developments in new on-line measurements with process control theory and practice will be crucial to the fullest possible development of chemical manufacturing. This is only one example of many future challenges in process analysis.

## **CHALLENGES AND OPPORTUNITIES FOR THE FUTURE**

Chemical measurements will continue to be challenged by the broad advances of the chemical sciences. It is not possible to overstate the future need for massively parallel, high-throughput, miniaturized, and widely distributed instrumental analyses, preferably with “smart instruments” that are self-calibrating and highly automated. Furthermore, a related need exists for massive automation in data reduction, storage, retrieval, and graphic presentation. The necessary devices will revolutionize the practice of medicine and the understanding of the life sciences, and they will provide chemists and chemical engineers with the tools for discovery and for process control.

At the start of the 21st century, we are witnessing a discernible shift from hypothesis-driven science and technology to information-driven science and technology. In the 21st century, the interaction of measurement science with theory, modeling, and simulation will play a central role in the acquisition of information and its conversion into useful knowledge. New fundamental knowledge is essential for advancement in the measurement sciences, particularly in nanoscale science and technology, which are at the heart of future advances in automated storage and retrieval of information. The measurement sciences correspond to a

convergent need in both the Human Genome Project and the quest for new materials. Increasingly, precise and quantitative measurements are equally essential to advancing the acquisition of fundamental knowledge.

The chemical world is often divided into “measurers” and “makers” of molecules. This division has deep historic roots, but it artificially impedes taking advantage of both aspects of the chemical sciences. Of key importance to all forms of chemistry are instruments and techniques that allow examination, in space and in time, of the composition and characterization of a chemical system under study. To achieve this end in a practical manner, these instruments will need to multiplex several analytical methods. They will need to meet one or more of 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.

The development of measurement tools of unprecedented specificity and sensitivity will be central to achieving a molecular-level understanding of complex systems that will allow molecular interactions and their time evolution to be fully understood. 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.

Additional instrumentation demands spring from the reduction in size of systems that must be studied to the microscale and nanoscale levels. This size reduction will require greatly increased instrumental sensitivity as well as new mathematical approaches to pattern recognition and graphics display. The need for new fundamental knowledge of interfacial and transport phenomena will be accentuated by the dramatic increase in the surface-to-volume ratio that will result from the corresponding reduction in sample size. 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.

Urgent expansion is needed for activities in the measurement sciences to achieve a variety of goals:

- Develop new concepts and associated instrumentation in five broad categories:
  1. High-performance instruments and measurements of unprecedented precision, sensitivity, spatial resolution, or specificity;
  2. Low-cost, robust instruments and measurements for monitoring and analyzing exceptionally small volumes, for real-time control of pro-

- cesses, or for detection of chemicals and biotoxins without physical contact;
3. High-throughput measurements, including informatics and mathematics for interpretation of large-volume data streams;
  4. Separation and analysis of chemical and biological mixtures of extreme complexity and heterogeneity;
  5. Determining the structural arrangements of atoms within noncrystalline chemical substances, and resolving how they change as a function of time, on any time scale.
- Integrate measurement science into the fundamental intellectual core of graduate education and training for scientists and engineers.

### WHY THIS IS IMPORTANT

The most fundamental question that anyone can ask when looking at a new material is, “What are the molecules (or ions, etc.) in it, and how much of each is there?” For a chemical scientist, this means discovering the molecular composition of all the components in some substance, their quantitative amounts, and their arrangement with respect to each other. The context of this discovery can be our own bodies, the swamp next door, the air on the highway, the white powder in an envelope, and, in the broadest context, the planet next door or a galaxy away. When we want to know more about other planets in our solar system, we devise instruments that can go to those planets and examine their chemical components. The instruments need to be able to detect and measure the chemicals that are present, and determine if they might indicate present or past life on those planets. Such tools let chemists and chemical engineers isolate, detect, and measure—so they can explore the chemical universe. The instruments that allow them to determine chemical structures permit them to identify the novel components of that universe, including those parts of it that humans themselves create.

In practical terms, detecting and measuring are critical to all aspects of human activity—to manufacturing, to our environment, to health and medicine, to agriculture, and to national security. Thus it is essential that chemical scientists continue to improve the tools and methods needed for this central scientific activity.

# Chemical Theory and Computer Modeling: From Computational Chemistry to Process Systems Engineering<sup>1</sup>

## **Some Challenges for Chemists and Chemical Engineers**

- Develop computer methods that will accurately predict the properties of unknown compounds.
- Develop reliable computer methods to calculate the detailed pathways by which reactions occur in both ground states and excited states, taking full account of molecular dynamics as well as quantum and statistical mechanics.
- Develop reliable force fields for molecular mechanics calculations on complex systems, including those with metallic elements.
- Invent computer methods to predict the three-dimensional folded structure of a protein—and the pathway by which folding occurs—from its amino acid sequence, so information from the human genome can be translated into the encoded protein structures.
- Devise experimental tests to establish the reliability of new theoretical treatments.

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<sup>1</sup>As part of the overall project on Challenges for the Chemical Sciences in the 21st Century, a workshop on Computing and Communications will lead to a separate report. The reader is urged to consult that report for further information. Also see *Mathematical Challenges from Theoretical/Computational Chemistry*, National Research Council, National Academy Press, Washington, D.C., 1995.

- Invent new computer tools and logistics methods to reduce significantly the time needed for commercializing new drugs.
- Invent new algorithms to globally optimize at the worldwide level the use of raw materials, energy, and environmental impact of chemical processes.
- Develop new and powerful computational methods, applicable from the atomic and molecular level to the chemical process and enterprise level, that will enable multiscale optimization.

The phenomenal increase in speed and computational power of computers—as well as their dramatic reduction in cost—has continued at an astonishing pace over the last decade. In terms of CPU speed, Moore's law implies that computing power should double every year or two,<sup>2</sup> a pattern that is expected to continue for at least 10 years into the future. At the same time, key advances in areas such as ultraviolet lithography techniques, nonleaking complementary metal oxide semiconductor (CMOS) transistors, and multiple instruction, multiple data (MIMD) computer architecture are already in place to support clock-speeds at the 10-GHz plateau with power requirements at 1 V or lower. In addition, the technology and software infrastructure now exist for researchers to routinely build large parallel supercomputing clusters using off-the-shelf commodity computers and networking components, thus increasing the impact of Moore's law by orders of magnitude. Finally, 10 years ago, few could envision how the dimension of communications—via the Internet—would enhance computing in what may have been the most revolutionary development in the late 20th century.

Chemistry and chemical engineering, like many other disciplines, are being profoundly influenced by increased computing power. This has happened in part by enhancing many existing computational procedures, providing a new impetus to quantum mechanical and molecular simulations at the atomic level, and optimizing processes and supply chain management at the macrosystem level. Furthermore, these computational tools have helped test new conceptual approaches to understanding matter and molecules. While we expect all these developments

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<sup>2</sup>Moore originally stated that "The complexity for minimum component costs has increased at a rate of roughly a factor of two per year," Moore, G.E., *Electronics*, 38 (8), 1965. This has been restated as "Moore's Law, the doubling of transistors every couple of years," (<http://www.intel.com/research/silicon/mooreslaw.htm>). There are two related laws: (1) The cost of a fabrication plant to make each generation of processors doubles in price from the previous one. (2) Since the discovery of the giant magnetoresistance (GMR) effect, the density of disk storage increases by a factor of 2 every 12 months. See also: Gelsinger, P., Gargini, P., Parker, G., Yu, A., *IEEE Spectrum*, October 1989.

to continue, the important challenge is likely to arise in dramatic growth of new computing needs. These needs are driven by the increasing shift in the chemical industry toward biotechnology products and pharmaceuticals, the emergence of industrially relevant nanotechnologies, the requirement to optimize existing large-scale commodity chemicals plants, and the increased size and complexity of many new problems and systems. Instruments used by chemists and chemical engineers are already substantially controlled by on-board computer systems, the complexity of which will increase with that of the purpose and use of the instruments.

Computational chemistry and process systems engineering play a major role in providing new understanding and development of computational procedures for the simulation, design, and operation of systems ranging from atoms and molecules to industrial-scale processes. The enormous span of scales of space and time that range from computational chemistry to process systems engineering can be visualized with the “chemical supply chain” shown in Figure 6-1. The supply chain starts with the set of chemicals that industry must synthesize and characterize at the molecular level. Subsequent steps aggregate these molecules into clusters, particles, and films—as single and multiphase systems that finally take the form of macroscopic mixtures. At the process engineering scale, the figure illustrates the design and analysis of production units that are integrated into a chemical process, which in turn is part of a site with multiple processes. Finally, this site is part of the commercial enterprise that is driven by business considerations. The multiple scales of this chain are a fact of life in chemical sciences and technology. To date, the field has neither sufficient tools nor enough trained people to pursue computational chemistry and chemical engineering across all these scales. The field will qualitatively change—in new insights, in what experiments are done and how chemical products and processes are designed—when this is achievable.

Advances in computing have facilitated major progress in computational chemistry and biochemistry, computational materials design, computational fluid dynamics, process synthesis, planning and scheduling, model-based process control, fault diagnosis, and real-time process optimization. This progress has been enabled by parallel advances in fundamental chemical physics theory, mathematics, operations research, and computer science—including computational techniques for simulation and optimization of chemical systems. This chapter shows how areas that span computational chemistry, from the atomic level to process systems engineering at the macrosystem level, are full of exciting computational challenges that await solutions from bright minds.<sup>3,4</sup>

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<sup>3</sup>*Impact of Advances in Computing and Communications Technologies on Chemical Science and Technology*, National Research Council, National Academy Press, Washington, D.C., 1999.

<sup>4</sup>*Mathematical Challenges from Theoretical/Computational Chemistry*, National Research Council, National Academy Press, Washington, D.C., 1995.

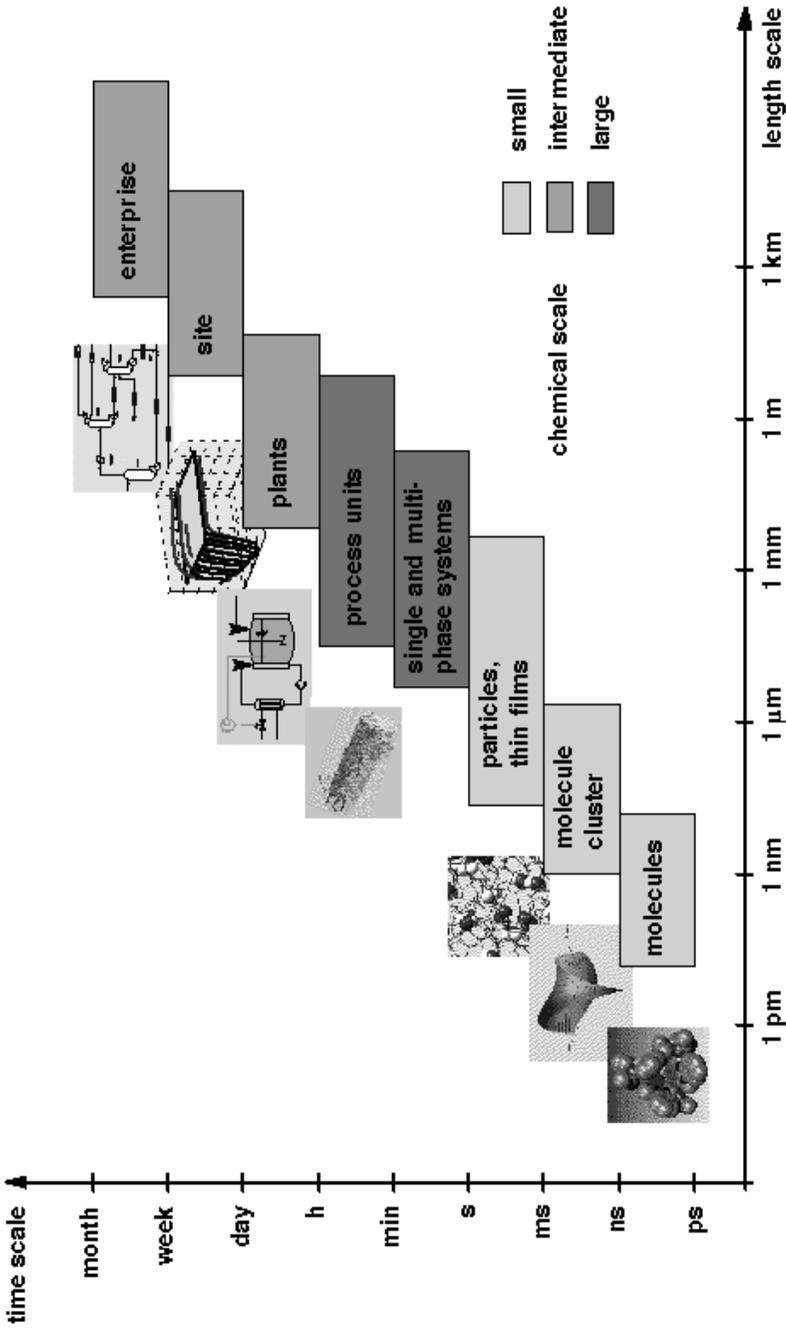


FIGURE 6-1 The chemical supply chain. Courtesy of Professor Wolfgang Marquardt.

## GOALS

Science proceeds by both experiment and theory. Simple experimental facts without a theory to interpret them do not satisfy our need for understanding. Indeed, many experimental measurements cannot be interpreted without theory, and as experiments probe phenomena and structures at ever smaller spatial and temporal scales, the role of theory in interpreting experiment increases. However, theory without experiment can lead to unrealistic dreams. The birth of modern science came when it was realized that truth is obtained from facts, not just from speculation. Theory validated by experiment runs through all of chemistry, and almost all its branches now use computers. Structures are determined by computer treatments of x-ray data, potential new drugs are analyzed by computer modeling, and even synthetic strategies to make a desired target molecule are developed using computer programs created for the purpose.

### Quantum Mechanics

The chemical sciences are built on a set of fundamental mathematical theories that have increasing utility as computational hardware and software become more powerful. As the basis for calculating the electronic structure of molecules, quantum mechanics permits calculations, often based on rational approximations, of structure and properties of molecules, and of reactivity and reaction mechanisms. The Schrödinger wave equation can in principle predict the electronic states of any chemical species, but in practice it can be applied only approximately to molecules of any significant size. A continuing, important goal is to devise better and more accurate ways to obtain predictions of molecular structures, bond energies, molecular properties, transition state structures, and energies for systems of increasing size.

Good approximate quantum calculations usually can be done reliably only for isolated molecules. Another important objective in this field is to develop methodologies for solvated molecules and molecules that are parts of membranes or other organized biological systems. Engineers are attempting to use quantum mechanical calculations to predict practical phenomena—for example, making and breaking of bonds in adhesion and fracture—that are based on electronic interactions. Additional goals are to learn how to accurately include heavier elements and to calculate the properties of molecules as a function of time, when they are interacting with other species.

Quantum calculations are the starting point for another objective of theoretical and computational chemical science, multiscale calculations. The overall objective is to understand and predict large-scale phenomena, such as deformation in solids or transport in porous media, beginning with fundamental calculation of electronic structure and interactions, then using the results of that calculation as input to the next level of a more coarse-grained approximation.

An important goal is to improve or supplement quantum mechanical methods in order to calculate reliably the energy and geometry of a transition state. This is one piece of information that can lead to the larger objective of predicting the rates of unmeasured reactions, but a second goal must also be met to achieve this. The accurate prediction of reaction rates also depends on our knowledge of dynamical properties of molecules and the dynamics of their sampling of accessible electronic, rotational, and vibrational states. Another goal is to predict the course of excited-state reactions, often initiated by adsorption of light. Such molecules do not traverse the lowest energy paths, and they usually form products that are different from those produced in ground-state reactions. Molecules that absorb light are transformed into various different excited states, depending on the energy of the light that is absorbed. Each excited state can in principle undergo a unique photochemical transformation. The development of successful theoretical treatments for such complex phenomena presents a substantial challenge. This goal also extends to the calculation of magnetic, optical, electrical, and mechanical properties of molecular and extended solids in both the ground and excited states.

Yet another related goal is to be able to predict the catalytic activity of a given surface for a particular reaction. Using computational quantum chemistry, it is becoming possible to predict with reasonable accuracy the energy barriers and transition states of molecules reacting on catalytic surfaces, thus leading to insights into reaction rates. This is enabling a new field of rational catalyst design, which offers the promise of designing and optimizing new catalysts computationally so that synthetic efforts can be focused on high-priority candidates.

### **Molecular Mechanics**

One tool for working toward this objective is molecular mechanics. In this approach, the bonds in a molecule are treated as classical objects, with continuous interaction potentials (sometimes called force fields) that can be developed empirically or calculated by quantum theory. This is a powerful method that allows the application of predictive theory to much larger systems if sufficiently accurate and robust force fields can be developed. Predicting the structures of proteins and polymers is an important objective, but at present this often requires prohibitively large calculations. Molecular mechanics with classical interaction potentials has been the principal tool in the development of molecular models of polymer dynamics. The ability to model isolated polymer molecules (in dilute solution) is well developed, but fundamental molecular mechanics models of dense systems of entangled polymers remains an important goal.

A particular goal of chemical theory is to predict protein structure from the amino acid sequence—to calculate how polypeptides fold into the compact geometries of proteins. One strategy is to develop methods (often based on bioinformatics) for predicting structures approximately and then refining the structures

using atomic-level molecular modeling methods. Molecular mechanics is also the theoretical approach employed in calculating how a proposed drug might bind into a protein.

### **Modeling and Simulation**

Modeling and simulation are extremely important tools in the chemical sciences. The understanding and engineering of complex chemical processes, such as combustion or atmospheric chemistry and transport, generally rely heavily and increasingly on modeling and computation. Recent advances in computing not only have enabled more accurate and reliable calculations, but they have also provided new tools for interpreting the output of the calculations. Modern computer graphics—including molecular graphics, simulations, and animations—have greatly enhanced the ability of scientists and engineers to understand and utilize the results of their computations.

Yet modeling can be no better than its assumptions. It often suffers from the problem that we cannot follow any computed process for a long duration (many time steps)—primarily because the computer time needed per time step is significant, but also because of the cumulative propagation of round-off errors. The typical time step is on the order of 1 femtosecond (i.e.,  $10^{-15}$  s) of real time for an atomically detailed molecular simulation. Consequently, modeling phenomena on the femtosecond time scale would require about  $10^3$  time steps, which is not difficult, and modeling on the picosecond time scale ( $10^6$  time steps) is fairly routine. However, many phenomena of interest (e.g., the time to fold a protein) are on the millisecond or larger time scale and would require  $10^{15}$  time steps or more. Another goal is to learn how to improve the calculations by overcoming these problems. One approach is to use stochastic approaches based on cleverly chosen Monte Carlo methods; another is to reduce the level of detail in the models for the molecules (so-called coarse grained models).

### **Statistical Mechanics and Fluid Mechanics**

Sometimes the theoretical or computational approach to description of molecular structure, properties, and reactivity cannot be based on deterministic equations that can be solved by analytical or computational methods. The properties of a molecule or assembly of molecules may be known or describable only in a statistical sense. Molecules and assemblies of molecules exist in distributions of configuration, composition, momentum, and energy. Sometimes, this statistical character is best captured and studied by computer experiments: molecular dynamics, Brownian dynamics, Stokesian dynamics, and Monte Carlo methods. Interaction potentials based on quantum mechanics, classical particle mechanics, continuum mechanics, or empiricism are specified and the evolution of the system is then followed in time by simulation of motions resulting from these direct

interparticle, stochastic, or fluid mechanical forces. The larger the size of the computation, the better the statistical representation of the system.

Statistical mechanics is the science that deals with average properties of the molecules, atoms, or elementary particles in random motion in a system of many such particles and relates these properties to the thermodynamic and other macroscopic properties of the system.<sup>5</sup> Use of statistical mechanics reflects the view that broad features of a system may be captured best as a description of the statistical distribution of the elements within a population rather than as a precise description of the elements themselves. One advantage of statistical mechanics is that a good model often reveals some underlying generality governing the system, thereby permitting analogies to be made between properties or behaviors that superficially are quite different. Simulations and statistical mechanics are key tools for physical chemists and engineers working on understanding rheological behavior, mass transport, modeling of microfluidic devices, flow of granular media, and behavior of dense particle suspensions.

At the next higher level of coarse-graining, fluid mechanics and other continuum mechanics methods are active arenas of theory and computation. For example, electrorheology and magnetorheology have provided tremendous impetus in the last decade. Efforts to determine the dependence of basic scaling on field strength and particle volume fraction quickly require answers to questions about material properties. The links between the thinking of chemical engineers studying transport and chemists designing and producing materials are crucial for progress. Granular media is another area where the clear interplay between science and technology is facilitating progress in solving sophisticated scientific questions that have immediate impact on technology and practice. From the viewpoint of computation and simulation, engineers working in granular media are addressing problems of flow and mixing (such as those arising in the processing of powdered pharmaceuticals); discrete computational approaches encompass particle dynamics, Monte Carlo, and cellular automata calculations.

### Spanning Length and Time Scales

Many of the problems cited above highlight the need for being able to bridge calculations across several length and time scales. It is thus worthwhile to consider this in some additional detail. For example, reactions involve changes in the molecules, and hence are inherently quantum mechanical in nature. But a reaction taking place in a solution at finite temperature implies that the reaction is influenced by a dynamic environment more pragmatically described by classical molecular simulation methods. Hence, a scale-bridging method is needed to allow the dynamics of the solvent around the reactants to influence the electronic

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<sup>5</sup>*Random House Webster's Unabridged Dictionary*, V2.2 for 16-bit Windows systems, copyright 1999, Random House, Inc.

structure of the reactants in various conformations, as well as the reactants influencing the motion of the solvent molecules around them. One solution is to perform molecular simulations with force fields calculated “on the fly” by quantum mechanical methods at each time step. Such “first principles” or *ab initio* molecular simulation methods are presently limited to fairly small numbers of atoms (around 100 to 1000) for rather short simulations (10 ps is a typical value). Other hybrid methods, which treat just the environment around reactants quantum mechanically, are less accurate in principle but allow much longer time scales and much larger spatial scales to be accessed, since the vast majority of the molecules are treated by classical molecular simulation.

The problem of spanning scales goes well beyond spanning from the electronic structure scale to the molecular (which might be thought of as the Ångström- or nanoscale). Chemical processes at the commercial scale ultimately involve spatial scales on the order of meters, and time scales (corresponding to processing times in reactors and separations equipment) ranging from seconds to hours and, in the case of many bioengineering processes involving fermentations, days or weeks. How do we connect phenomena at the electronic and molecular scale to the commercial chemical process scale?

In some cases, the connection is trivial: for low-molecular-weight molecular systems, properties calculated at the electronic structure level (e.g., reaction rates, and free energies of formation and reaction) or at the molecular simulation level (e.g., the so-called critical constants, and transport properties such as viscosity) can be used directly at the process scale as input data for process models. However, for complex molecules (such as polymers and proteins) the properties at the molecular level are not decoupled from the process level. For example, flow at process level can result in changes in the conformation of the molecules, which in turn changes the properties of the molecules. In such cases, the problem of developing accurate molecular modeling methods that will span the scales from electronic to molecular to mesoscopic to macroscopic (the process scale) cannot be avoided. Since such complex molecules and their processing are the focus of the modern chemical, pharmaceutical, and materials industries, it is imperative that the problem of developing effective multiscale modeling methods be solved. It is currently one of the most active research focuses of the molecular modeling community. It is also a major focus of nanotechnology modeling efforts, since in such systems the need to connect nanoscale structure to macroscale functionality is even more apparent.

Making the “scale-up” connection between the electronic and molecular structure of molecules and their macroscopic properties, and the design of processes to manufacture them, is one half of the story. The other half is making the connection “scale-down”—from specification of a process-level manufacturing need (e.g., a solvent with better properties) to the design of a molecule that meets the need. Harnessing these yet-to-be-developed methods and combining them with state-of-the-art process modeling and optimization tools will result in inte-

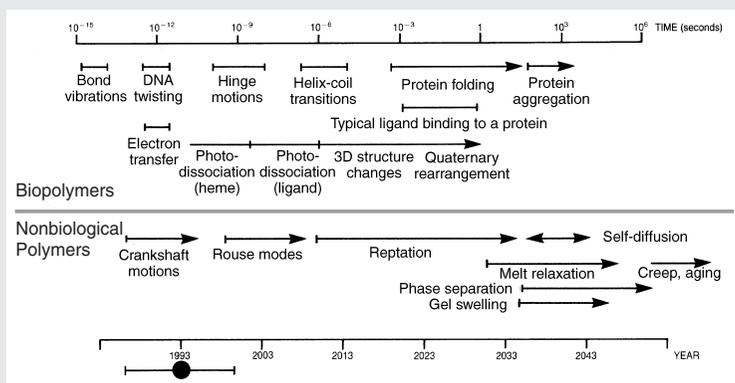
grated process and product design: the ability to computationally design and optimize products (e.g., chemicals, drugs, materials) as well as the manufacturing processes to make them. The molecular modeling and process design communities recognize that, with the continued rapid pace of computer hardware, software, and algorithmic advances, this goal is now accessible in the next decade or two. Hence, conferences are beginning to spring up whose main goal is to bring together members of these communities to learn from each other. Cross-fertilization between the fields has led to computational chemistry methods (e.g., simulated annealing) crossing over to the process design community, just as techniques from the process design community (e.g., mathematical programming methods) have crossed over to the protein folding community.

### The Problem of Time Scales in Molecular Simulation

Brute-force classical molecular dynamics simulation will not span the time scales present in complex molecular systems, even with fully efficient implementation on the world's fastest parallel supercomputers. This time scale problem was captured well by Ken Dill in 1993.<sup>6</sup> Although this scheme did not fully take into account the impact of massively parallel computers (by which the current generation of ~10 teraflops computers theoretically increase the level of computing 1,000- to 10,000-fold over workstations), the essential problem of simulating over long periods of time relative to the shortest time scale motion is not fundamentally changed even by recent advances in parallel supercomputing. While parallel supercomputing makes it possible to span larger spatial scales rather easily, spanning larger time scales remains a fundamental difficulty. To be more concrete, there are about 30 million seconds in a year, and the maximum speed at which messages can be passed between any two processors on a parallel supercomputer is roughly 10,000 per second. Hence, even if the time to compute forces could be reduced by sufficient parallelization to essentially zero, a molecular dynamics simulation could not execute more than  $3 \times 10^{11}$  time steps per year; in practice, it will be considerably less. When a calculation is limited by the time required to pass messages, it is referred to as communications-limited. Thus, with a time step of  $10^{-15}$  s, in a year of computing the most one could hope to achieve is around  $10^{-4}$  s of real time. This conclusion highlights the need to develop theoretically sound methods for spanning the many time scales present in the molecular simulation of complex systems (such as proteins and polymers).

<sup>6</sup>H.S. Chan, and K.A. Dill, *Physics Today*, 46 (2): 24-32 Feb. 1993.

How well has Dill's prediction held up? In 2000, the first ever microsecond-long molecular dynamics simulation of protein folding was reported. It required 750,000 node hours (equal to the product of the number of hours times the number of processors) of computer time on a Cray T3 supercomputer. According to Dill's prediction, this length of simulation was not to be expected until around 2010. However, as noted above, Dill's analysis does not take into account large-scale parallelization—which, unless the computation is communications-limited, will effectively increase the speed of a computation in proportion to the number of processors available.



Time scales for various motions within biopolymers (upper) and nonbiological polymers (lower). The year scale at the bottom shows estimates of when each such process might be accessible to brute force molecular simulation on supercomputers, assuming that parallel processing capability on supercomputers increases by about a factor of 1,000 every 10 years (i.e., one order of magnitude more than Moore's law) and neglecting new approaches or breakthroughs. Reprinted with permission from H.S. Chan and K. A. Dill. *Physics Today*, 46, 2, 24, (1993).

## PROGRESS TO DATE

Important insights have been developed using approximate methods that were not highly precise quantitatively, and excellent high-level methods for solving the Schrödinger equation have been developed, but the methods still have used approximations. A Nobel Prize in 1998 went to John Pople and Walter Kohn for their different successful approaches to this problem. Earlier methods used many

different parameters derived from experiment, but current so-called *ab initio* methods as pioneered by Pople are essentially free of such experimentally derived parameters. With the current methods, systems of 5 to 20 common atoms are handled well. Density-functional theory (DFT) as developed by Kohn is also moderately successful with larger systems, and with more unusual atoms.

In molecular mechanics, force fields and sampling methods used in the calculations are being improved continually, but they are not yet good enough that atomic-level refinement of protein structures is feasible on a robust and routine basis. It is unclear what the relative contribution of force field and sampling errors are to the problem. Similar comments apply to the prediction of protein-ligand binding. The protein-folding problem is thus currently being approached mainly by analogy, using data from existing protein structures to derive various folding rules. The field of *ab initio* theoretical protein folding—prediction of full three-dimensional protein structure using a combination of an optimization algorithm to minimize energy with an explicit force-field representation of the functional groups in the protein—is a computationally intensive approach that has recorded some successes in protein structure prediction.<sup>7</sup> *Ab initio* protein-folding approaches are the only methods capable of predicting fundamentally new structures in proteins (i.e., substructures not previously found in any experimentally measured protein structures). One forefront area of research at the interface of polymers and biology is the synthesis (by genetic engineering) of synthetic proteins/biopolymers containing building blocks other than the usual 20 amino acids, including inorganic species such as silicon. *Ab initio* protein-folding approaches offer routes to predicting the properties of such biopolymers.

Initially, most theoretical methods calculated the properties of molecules in the gas phase as isolated species, but chemical reactions are most often carried out in solution. Biochemical reactions normally take place in water. Consequently, there is increasing interest in methods for including solvents in the calculations. In the simplest approach, solvents are treated as a continuum, whose average properties are included in the calculation. Explicit inclusion of solvent molecules in the calculation greatly expands the size of the problem, but newer approaches do this for at least those solvent molecules next to the dissolved species of interest. The detailed structures and properties of these solvent molecules affect their direct interaction with the dissolved species. Reactions at catalytic surfaces present an additional challenge, as the theoretical techniques must be able to handle the reactants and the atoms in the surface, as well as possible solvent species. The first concrete examples of computationally based rational catalyst design have begun to appear in publications and to have impact in industry.

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<sup>7</sup>The use of the term *ab initio* in the context of protein folding should not be confused with its use to describe *ab initio* quantum chemistry calculations. In both cases, *ab initio* is meant to convey the idea of “from first principles,” but the starting point and theoretical framework are different for each.

In the area of collective properties, simulation methods have been developed over the past decade and a half that make it possible to predict the phase equilibria of systems directly from force fields, dramatically widening the applicability of molecular simulation for process-engineering calculations. Phase equilibria of various kinds (vapor-liquid, liquid-liquid, fluid-solid) lie at the center of most of the separation techniques (e.g., distillation and crystallization) commonly used in the chemical industry. The last decade has also seen dramatic improvements in molecular simulation methodologies—largely based on stochastic methods—for overcoming the long relaxation times inherent in the equilibration of polymers and similar complex materials. A recent international comparative study of the industrial application of molecular modeling in the chemical, pharmaceutical, and materials industries in the United States, Europe, and Japan gathered information from over 75 sites; the report documents some of the remarkably diverse ways in which molecular modeling methods are successfully impacting industry today.<sup>8</sup> Given the limitations of today's tools, the future for integrated molecular-based product design and process-level design and optimization is very bright indeed.

### **Goals in Process Systems Engineering, and Progress to Date**

Process systems engineering is the study of the processes used in manufacturing. It encompasses all aspects of the design, construction, control, and operation of the chemical processes used in chemical manufacturing. The goal of process systems engineering remains the understanding and development of tools for the advantaged synthesis, analysis, optimization, evaluation, design, control, scheduling, and operation of chemical process systems consistent with new societal and economic objectives and constraints. This is true for all processes—no matter what the chemistry or biochemistry, whether isolated or in supply chain networks, dedicated or general purpose, batch or continuous, and whether micro-scale or macroscale. This goal requires the further creation and exploitation of a science base that includes novel representations of the underlying chemical and physical phenomena, computationally efficient formulation and solution methods, and the expansion of and incorporation of advanced engineering expertise and judgment. As discussed below, two major objectives in process systems engineering are the creation or invention of new processes (process synthesis), and the systematization of decision-making with prediction of systems performance (modeling and optimization).

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<sup>8</sup>The report is available on the Internet at <http://itri.loyola.edu/molmodel>.

*Process Synthesis*

Creation of new processes for building new plants or retrofitting existing facilities is a key area for addressing the goals of process systems engineering cited above. The major reason is that process synthesis deals with the systematic generation and search of alternatives that can potentially lead to major structural discoveries and modifications. Significant progress has been made in the development of systematic techniques for the synthesis of energy recovery networks, distillation systems (including azeotropic separations), and reactor networks. For synthesizing process flow sheets that integrate these subsystems, hierarchical decomposition and superstructure optimization have emerged as two major approaches. In the design of multiproduct batch plants, progress has been made with mathematical programming models that integrate scheduling as part of the design decisions.

In the future we will see the application of synthesis techniques to new processes that involve greater use of more abundant or renewable raw materials, and greater reuse of materials such as carbon dioxide, salts, tars, and sludges, which are currently generally disposed of. Exploiting some of these alternative raw materials and chemistries may involve greater energy input than required for raw materials presently in use, and the source and impact of any such increased energy requirement must also be carefully considered. At the same time, pressures to increase reaction selectivity will continue unabated.

Process synthesis is the invention of chemistry-implementing processing concepts. It is a creative open-ended activity characterized by a combinatorially large number of feasible alternatives. Process synthesis defines the overall structure of the manufacturing process and identifies and designs the processing equipment to be employed and specifies how they are to be interconnected. The number of potential feasible process designs is in general very large, and selecting the right process structure generally determines most of the economic potential of a new or retrofitted chemical process. In recent industrial experience, energy reductions of 50% and overall cost reductions of 35% using systematic process synthesis techniques have been achieved. Nevertheless, a significant need remains for even better approaches.

Some success has been achieved in developing systematic process synthesis methods based on recursive hierarchical means-ends analysis architectures adapted from artificial intelligence research. These have been greatly aided by the recent development of new representations of the underlying physical science and thermodynamic knowledge that define the forces generally engaged in chemical reaction and separation processes. Exploiting these representations—problem-solving strategies that focus primarily on the processing tasks to be accomplished rather than the equipment to be employed—has proven to be particularly effective in creating novel superior designs.

The chemical process synthesis problem might also be formulated as an optimization over all feasible process structures. In principle, if we employed all different possible approaches to implement some desired chemistry—including all possible different reactor configurations, all possible different separation and purification schemes, techniques, and equipment, and all interconnections among these potential units in one gigantic tentative process flow sheet—and if we then subjected such a superstructure to economic optimization constrained by environmental, safety, and other criteria (during which process inferior equipment and interconnections were eliminated), the best manufacturing process in terms of both structure and the design of each surviving piece of equipment would emerge. This, of course, is a massive and extremely difficult optimization problem involving a mixture of continuous, integer, and logical variables and relationships. However, new mathematical techniques such as generalized disjunctive programming and global optimization, combined with the tremendous increases in available computing power made possible through large clusters of fast independent processors, give hope that this superstructure optimization approach to chemical process synthesis may be practical in the near future.

### *Modeling and Optimization*

The chemical industry can largely be viewed as being composed of two major segments. One is the “value preservation” industry that is largely based on the large-scale production of commodity chemicals. The other is the “value growth” industry that is based on the small-scale production of specialty chemicals, biotechnology products, and pharmaceuticals. For the chemical industry to remain strong, it is essential that these two segments be competitive and economically strong. The “value preservation” industry must be able to reduce costs, operate efficiently, and continuously improve product quality, thereby making process simulation and process optimization its key technologies. The “value growth” industry must be agile and quick to market new products, making supply chain management one of its key technologies. In both cases, major challenges over the next two decades will be to gain a better understanding of the structure and information flows underlying the chemical supply chain of Figure 6-1, and to develop novel mathematical models and methods for its simulation and optimization.

In the past, most of the modeling and optimization activity has taken place in isolated parts of the chemical supply chain. In chemical engineering it has been mostly at the level of process units and plants, but more recently it has been moving in two opposing directions—the molecular and the enterprise levels. In computational chemistry, the modeling research has been directed at the molecular level and is increasingly moving toward the atomic and quantum scale, as discussed in the previous sections. Developments in planning and scheduling are being increasingly directed to address the optimization of the supply chain at the

enterprise level. Major difficulties in developing mathematical models that integrate the various parts of the chemical supply chain result from the huge differences in length and time scales in the supply chain and the number of chemical species considered at each level. Furthermore, at the longer scales, new situations can arise that may not be reliably predicted from the basic models.

### **Process Simulation: A Revolution**

Process simulation, which emerged in the 1960s, has become one of the great success stories in the use of computing in the chemical industry. For instance, steady-state simulation has largely replaced experimentation and pilot plant testing in process development for commodity chemicals, except in the case of reactions having new mechanisms or requiring new separation technologies. Tools for steady-state process simulation are nowadays universally available to aid in the decisions for design, operation, and debottlenecking; they are part of every process engineer's toolkit. Their accuracy and predictive ability for decision-making is widely accepted to make routine plant trials and most experimental scale-up obsolete in the commodity chemicals industry.

Dynamic simulation plays a dominant role in the design of training simulators for operators. As with aircraft simulation, these programs allow operators to deal with disturbances, start-ups, and upsets that go beyond conventional regulatory control. For hazardous processes, they are a requirement for operator certification on distributed control systems. Environmental, safety and hazard, and operability studies are often handled through steady-state and dynamic simulation tools. In short, process simulation is the engine that drives decision-making in process engineering. It is the accepted "virtual reality" of the process industries.

Some recent applications have benefited from advances in computing and computational techniques. Steady-state simulation is being used off-line for process analysis, design, and retrofit; process simulators can model flow sheets with up to about a million equations by employing nested procedures. Other applications have resulted in great economic benefits; these include on-line real-time optimization models for data reconciliation and parameter estimation followed by optimal adjustment of operating conditions. Models of up to 500,000 variables have been used on a refinery-wide basis.

Off-line analysis, controller design, and optimization are now performed in the area of dynamics. The largest dynamic simulation has been about 100,000 differential algebraic equations (DAEs) for analysis of control systems. Simulations formulated with process models having over 10,000 DAEs are considered frequently. Also, detailed training simulators have models with over 10,000 DAEs. On-line model predictive control (MPC) and nonlinear MPC using first-principle models are seeing a number of industrial applications, particularly in polymeric reactions and processes. At this point, systems with over 100 DAEs have been implemented for on-line dynamic optimization and control.

While the developments described above are currently implemented and available, significant remaining issues are being investigated to further improve the capability of process simulators. One example is the use of object-oriented approaches to integrating models from different sources and vendors in a single simulation. Another challenge is combining partial differential equation models with DAE and algebraic process models, which will require parallel computations to solve models with millions of variables. Finally, nonlinear optimization algorithms are needed that can handle very large models as well as discrete variables for performing topology optimization in process flow sheets.

To tackle these problems successfully, new concepts will be required for developing systematic modeling techniques that can describe parts of the chemical supply chain at different levels of abstraction. A specific example is the integration of molecular thermodynamics in process simulation computations. This would fulfill the objective of predicting the properties of new chemical products when designing a new manufacturing plant. However, such computations remain unachievable at the present time and probably will remain so for the next decade. The challenge is how to abstract the details and description of a complex system into a reduced dimensional space.

Another important aspect in the modeling and optimization of the chemical supply chain is the description of the dynamics of the information and material flow through the chain. This will require a better understanding of the integration of R&D, process design, process operation, and business logistics. The challenge will be to develop quantitative models that can be used to better coordinate and optimize the chemical enterprise. Progress will be facilitated by new advances in information technology, particularly through advances in the Internet and by new methods and mathematical concepts. Advances in computer technology will play a central role. Fulfilling the goal of effectively integrating the various functions

(R&D, design, production, logistics) in the chemical supply chain will help to better meet customer demands, and effectively adapt in the new world of e-commerce. Concepts related to planning, scheduling, and control that have not been widely adopted by chemical engineers should play a prominent role in the modeling part of this problem. Concepts and tools of computer science and operations research will play an even greater role in terms of impacting the implementation of solutions for this problem.

### **Supply-Chain Management Increases Profitability of the Chemical Industry Through Computer Tools**

New optimization tools, information management systems, and the Internet are revolutionizing supply-chain management in chemical companies. The objective of these tools is not only to help manage more effectively the flow of materials from their production facilities to their distribution centers, but also to incorporate the suppliers and the customers. Instead of running businesses from the inside out, forward thinking companies are integrating their business processes to run the business the way their customers demand: from the outside in. The ultimate winners in this new world will be the ones who manage their supply chains more efficiently than their competitors, harness the customer loyalty factor, and find ways to facilitate business transactions. Making the customer and the other business partners more profitable is the new way to compete in the chemical industry, where many products rapidly become commodities. From simple ways to reduce the cost of each transaction, to working together to reduce overall inventories, to true collaboration of business processes such as product design, logistics management, manufacturing execution, product marketing, and overall management, the use of advanced computer and optimization tools and process models deployed through the Internet will give those companies a significant competitive advantage.

Supply-chain management can be applied at three major levels: strategic planning, tactical planning, and production scheduling. Furthermore, its integration can lead to new business practices such as improved "capability to promise" in the sales of products. An example of strategic planning is the integration of a single product through the entire supply chain, from raw materials delivery, through manufacturing, to delivery to customers. Major decisions at this level include rationalizing the distribution network, building new plants, or evaluating new markets. This is in contrast to tactical planning, which involves developing an operational plan, meeting capacity constraints, and developing inventory and overtime strategies to increase the efficiency in the supply chain. BASF per-

formed a corporate network optimization of packaged finished goods in North America. There were 17 operating divisions with multiple, heterogeneous systems: 25,000 stockkeeping units (SKUs), 134 shipping points, 15,000 ship-to locations, 956 million pounds shipped direct to customers, and 696 million pounds shipped to customers through distribution centers. By using optimization tools BASF reduced transportation and facility costs by 10%, next-day volume delivery increased from 77% to 96%, the number of distribution centers was reduced from 86 to 15, generating \$10 million per year savings in operating costs (personal communication, Dr. Vladimir Mahlaec, Aspen Technology).

An example of production scheduling involves scheduling a plant in continuous time to optimize sequencing, while providing an executable production schedule. This problem is complicated by the fact that it must take into account forecast and customer orders, inventories of raw material, intermediates and finished goods, facility status, manufacturing information, rates, facility preferences, and recipes. Pharmacia-Upjohn was faced with such a problem in the scheduling of a fermentation process. Using modern software, schedules were generated for 6 days of production. The major benefit was an effective and flexible computer tool for rescheduling that can readily accommodate changes in customer orders.

Finally, an interesting trend in supply-chain management is improving business practices by providing capabilities to improve service for customers. One such concept is "capability to promise." The idea is not just to ensure that the product is available, but that the supply chain is capable of delivering the product. This involves, for instance, capability to rapidly change the schedule to accommodate the customer order and interact with the active plant schedule. Such a system was developed at Celanese Fibers, which is integrated with a Customer Order System and enabled via a Web browser.

## CHALLENGES AND OPPORTUNITIES FOR THE FUTURE

### Chemical Theory and Computation

Faster and cheaper computers will extend the range of high-level methods. Improvements in DFT functionals will improve the accuracy of DFT calculations. One specific challenge will be to derive density functional theory from fundamental theory in a way that reveals how to incorporate successive approximations for the exchange and correlation terms. Some work on high-level methods with better scaling may allow more immediate extension of high-accuracy calculations to larger systems. Combining quantum mechanical and molecular

mechanics methods will allow very large systems to be treated using quantum methods in the reactive core and force fields for the remainder of the systems, for example in enzymatic chemistry. Many specific needs can be identified:

- methods to simulate quantum molecular dynamics in condensed systems without approximating the system as a quantum system coupled to a classical bath. This is not now possible although there has been some progress toward this end in the treatment of simple physical models. This is a development that will benefit greatly from the development of practical quantum computers.

- development of methods to bypass the problem of multiple time scales in molecular dynamics. This difficulty is particularly egregious in the protein-folding problem.

- methods for the efficient sampling of rough energy landscapes such as those found in proteins. Because of high energy barriers in such systems, most of the time is spent sampling energy basins near the starting configuration. The development of efficient methods is required for the determination of structural and thermodynamic properties as well as for efficient refinement of protein structure.

- accurate polarizable force fields for peptides, water, etc. Improved force fields explicitly incorporating polarization are being developed. Until rapid *ab initio* molecular dynamics methods exist, such force fields are required for the simulation of chemical systems with chemical accuracy.

- to understand the kinetics of protein folding from a mechanistic point of view. Abstract schemes have been proposed, but there is much yet to do before this goal is realized.

- to develop methods for understanding and predicting energy transfer, electron transport, and the entirely new quantum effects involving coherence that arise in nanoscale devices.

- to develop the statistical mechanics of fluids and fluid mixtures—for example, to obtain improved understanding of associating fluids, hydrophobicity, and ionic systems.

- to develop computational tools for solid-state problems, including calculation of magnetic, optical, electrical, and mechanical properties of molecular and extended solids in both ground and excited states.

- to correlate theoretical predictions with experimental results, designing experiments specifically to test various theoretical predictions. As this is done, and is successful, the role of mathematical theory in chemistry will increase in value.

### **Process Systems Engineering**

A number of major challenges exist in process systems engineering in which computing will play a major role. These can be grouped by major areas of application:

- **Process and Product Design.** The traditional process design will be expanded to include product design as an integral part of this area. Within the commodity chemicals industry major challenges that will be addressed include process intensification for novel unit operations, and design of environmentally benign processes. Areas that are likely to receive increased attention due to the growth in new industries include molecular design, synthesis of microchips, smart materials, bioprocess systems, bioinformatics, and design and analysis of metabolic networks.

- **Process Control.** The traditional process control will be expanded toward new applications such as nonlinear process control of biosystems. However, in the commodity chemicals industry there will be increased need for synthesizing plantwide control systems, as well as integrating dynamics, discrete events, and safety functions, which will be achieved through new mathematical and computer science developments in hybrid systems.

- **R&D and Process Operations.** The traditional area of process operations will expand upstream and downstream in terms of integrating R&D as well as logistics and distribution functions. Areas that are likely to receive increased attention include logistics for new product development, planning and supply chain management, real-time scheduling, and synthesis of operating procedures (safety).

- **Integration.** As is also described below, the integration of several parts of the chemical supply chain will give rise to a number of challenges, such as multiscale modeling for molecular dynamics, integration of planning, scheduling and control (including Internet based), and integration of measurements, control, and information systems.

Progress in these areas will require a number of new supporting tools that can effectively handle and solve a variety of mathematical models involving thousands and millions of variables. These supporting tools in turn will require that chemical engineers become acquainted with new advances in numerical analysis, mathematical programming, and local search techniques.

- There is a need for large-scale differential-algebraic methods for simulating systems at multiple scales (e.g., fluid mechanics and molecular dynamics), a capability that is still at a very early stage.

- There is a need for methods for simulating and optimizing models whose parameters are described by probability distribution functions, a capability that is in its infancy.

- There is a need for advanced discrete-continuous optimization tools that can handle mixed-integer, discrete-logic, and quantitative-qualitative equations to model synthesis and planning and scheduling problems.

- There is a need for methods that can determine global optima for arbitrary nonlinear functions, and that can handle extremely large nonlinear models for real-time optimization (on the order of millions of variables).

- There is a need for improved modeling tools to accommodate heuristic and qualitative reasoning.
- There is a need for hierarchical computations for conceptual design, which will require knowledge of new developments in computer science.
- There is a need for information-modeling tools, which will become increasingly important for supporting integration problems as well as teamwork.

Finally, there are new potential applications from software and Internet-based computing. While the former is likely to be most relevant for a few specialists, the demand for software development may increase as chemistry and chemical engineering move to new areas in which there are no standard software packages. For Internet-based computing an exciting possibility will be to share more readily new software developments directly from the developers, bypassing the commercial software vendors. Another area of sharing leading to powerful new computational opportunities in the chemical sciences is the use of peer-to-peer computing in the form of sharing unused cycles on small computers. We can do very large-scale computations on networks of personal computers, as is being done in studies of protein folding<sup>9</sup> and molecular docking.<sup>10</sup> The potential here is to tackle computational problems of unprecedented size and complexity, with a relatively low investment in the actual computational resources.

### Scientific Computing

Advances in scientific computing will help to address some of the challenges in computational chemistry and process systems engineering, particularly computational tasks that scale exponentially with size. While single-threaded execution speed is important and needed, coordination of multiple instruction multiple data (MIMD) computer systems is rapidly becoming the major challenge in scientific computing. The optimal parallel organization is application dependent: synchronous systems execute multiple elementary tasks per clock cycle while asynchronous models use clusters, vector units, or hypercubes. Although work in automatic task parallelization has made significant progress, the major issues in scientific high-performance computing are likely to be identification of suitable hardware architectures, algorithms to reformulate problems into a sequence of parallelizable subtasks with the “weakest possible” couplings, and nondeterministic procedures with statistical properties. On the positive side, parallel computing is becoming almost routine as individual researchers, groups, universities,

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<sup>9</sup><http://www.stanford.edu/group/pandegroup/Cosm/>; V.S. Pande and D.S. Rokhsar, *Proceedings of the National Academy of Sciences*, U.S.A. 96, 9062-9067, 1999; V. S. Pande, A. Y. Grosberg, T. Tanaka, and D. S. Rokhsar, *Current Opinions in Structural Biology*, 8:68-79, 1997.

<sup>10</sup><http://www.chem.ox.ac.uk/curecancer.html>; Robinson, Daniel D.; Lyne, Paul D.; Richards, W. Graham, *J. Chem. Inf. Comput. Sci.*, 40(2), 503-512, 2000.

and companies embrace low-cost cluster parallel computers made from commodity off-the-shelf processors and network interconnects. From a computational science point of view, however, this multiplies the complexity of delivering higher performance computational tools to practicing researchers. Even when the number of parallel supercomputer vendors peaked in the mid-1990s, the number of manufacturers, processors, and network architectures was limited to a handful of such systems; by contrast, the number of possible cluster configurations is enormous.

Beyond parallelization, the major thrust of high-performance computing today is computational grids, modeled after the electrical power grid, in which the computational resources of a large number of sites are combined through wide area networks into a computational metaresource. Significant scientific and technical obstacles associated with the grid computational environment must be overcome, since grids embody all the complexity of parallel computers with additional difficulties such as distributed ownership of resources, multiple and wide-ranging network latencies, and heterogeneous architectures, to name just three. Resolution of these obstacles is one of the major thrusts of computational science research today. Nevertheless, assuming these obstacles can be overcome, grid computing offers the possibility of solving the largest scale problems confronting the computational chemistry and process engineering communities in the most cost-effective way. They can also facilitate collaboration between groups with complementary expertise that can share their capabilities while maintaining control over them. One can foresee the day when integrated process/product design/optimization (IPPDO) is performed on a wide area grid in which dedicated servers perform needed parts of the overall calculation, with the most compute-intensive computations being executed on the highest performance nodes of the grid.

As the sophistication of computation approaches increases, and the desire to integrate product and process design and optimization becomes reality, we anticipate that large-scale computations will be required that may last for days or weeks (even on the fastest computational resources) and that these computations will require intervention and redirection (known as computational steering) by the experts managing the computation. Computational steering is a relatively new field that is being applied in such areas as global climate modeling. Enabling computational steering requires the development of appropriate visualization tools that communicate the relevant information to the users, and interfaces to the computation that enable quantities and methods to be changed. Tools specific to the integrated IPPDO application will need to be developed.

Another new capability whose impact is still somewhat difficult to predict is wireless computing. One area that is likely to benefit is in the integration of measurements, control, and information systems. Wireless computing may also play an important role in computational steering of long computations described above, since examining the state of a computation, consulting with colleagues, and steer-

ing the computation can all be envisaged as taking place on an appropriately enabled handheld device. Many of these tools exist in a disconnected and primitive form today: Much of the challenge lies in integrating the tools and adapting them for the IPPDO application.

### WHY ALL THIS IS IMPORTANT

In the final analysis, basic understanding of chemistry will require successful theoretical approaches. For example, in our picture of the exact pathways involved in a chemical reaction there is no current hope that we can directly observe it in full molecular detail on the fast and microscopic scale on which it occurs. As discussed in Chapter 4, our ability to make a detailed picture of every aspect of a chemical reaction will come most readily from theories in which those aspects can be calculated, but theories whose predictions have been validated by particular incisive experiments.

When we have the information from the sequencing of the human genome, and want to understand the properties of those proteins that are coded by some of the genes but not yet known experimentally, we need to solve the protein-folding problem. Then we can translate the gene sequence—which specifies the sequence of amino acids—into the three-dimensional structure of the unknown protein.

For practical applications, good effective theories and computational tools are invaluable. We want to calculate the properties of molecules that have not yet been made, to select a likely medicine for synthesis. We want to be able to calculate what catalyst would best speed a particular reaction with selectivity, so that catalyst can be created and used in manufacturing. We want to calculate the properties of organized chemical systems, nanometer-sized particles, and aggregates whose properties can be valuable in computers and in other electronic devices. We need to develop new and powerful computational methods that span from the atomic and molecular level to the chemical-process and chemical-enterprise level in order to allow their effective integration for multiscale simulation and optimization. We want to synthesize energy-efficient and environmentally benign processes that are cost effective. We want to manage networks of plants that eliminate inventories and can be operated in a safe and responsive manner. With increasingly powerful computers and better software, these goals seem within reach in the future, and they will greatly enhance our capabilities—both in basic and applied chemistry and in chemical engineering.

As discussed above, simulation and modeling are central components of process engineering. Improvements in these techniques will permit the design of much more efficient processes and facilities. Integrating the current and future capabilities of computational chemistry and process engineering will result in improved materials, chemicals, and pharmaceuticals; yield more efficient environmentally benign processes to manufacture them; and accomplish this while providing greater financial return.

## The Interface with Biology and Medicine<sup>1</sup>

### **Some Challenges for Chemists and Chemical Engineers**

- Understand fully the chemistry of life, including the chemistry of the brain and memory.
- Invent and learn to manufacture effective antiviral agents and antibiotics to fight all serious diseases, including those caused by drug-resistant pathogens.
- Invent medicines that go beyond treatment to provide cure or prevention of life-limiting conditions and diseases such as cancer, Alzheimer's disease, mental illness, and diabetes.
- Invent better ways to deliver drugs to their targets, including devices that can function as artificial organs.
- Learn how genetic variation among individuals will affect their responses to particular medicines.
- Invent biocompatible materials for organ replacements and for artificial bones and teeth.

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<sup>1</sup>As part of the overall project on Challenges for the Chemical Sciences in the 21st Century, a workshop on Health and Medicine will lead to a separate report. The reader is urged to consult that report for further information.

- Invent improved diagnostic methods so that diseases can be detected, identified, and treated at an early stage.
- Create food additives that protect and enhance our diets with unquestioned safety.
- Learn how gene expression is controlled in living cells and how we can affect that process with small-molecule medicines.
- Learn why enzymes are so effective, so we can design artificial biomimetic catalysts that work as well as the best enzymes.
- Extend our chemical understanding of how life might arise spontaneously, on earth or elsewhere.
- Make organized chemical systems that imitate the functioning of biological cells.

## GOALS

The goal of fundamental science at the interface of chemical sciences and biology is to understand life in chemical terms. Our ability to accomplish the translation of biology into chemical terms is closely related to our fundamental understanding of life's machinery. Decoding these mysteries and producing a detailed molecular picture of how things work is a critical step. However, for most people, the real impact comes when we can use that understanding to improve our lives. Nowhere has the role of chemical sciences been better illustrated than in the discovery, development, and production of new medicines and ways in which we can more selectively deliver these medicines to the organ or tissue where they are needed. This fundamental understanding of what chemical transformations occur in living creatures, how these chemical transformations are regulated, and how they respond to extracellular stimuli is also critical to developing semisynthetic tissues and organs as replacements for damaged organs, to gene therapy, and to solving a host of clinical problems. In addition, these chemical tools will provide the basis for improvements in the productivity of agriculture in both animal and plant production systems. Most directly, advances in the chemical sciences will be essential for the prevention, diagnosis, and treatment of disease.

## Underlying Science

The mechanisms of life are revealed when we understand their molecular details. Moreover, molecular understanding of biology plays the major role in

guiding drug discovery, and molecular-level understanding of biology is fundamental in developing diagnostic methods.

Nature is a highly innovative chemist, and we know only a small fraction of the universe of natural products. Currently, about half of the most widely prescribed drugs in the United States are either small-molecule natural products, such as penicillin, or synthetic molecules that are based on natural products but have better properties. The other half are products of the creative imagination of medicinal chemists. Nature's genetic and chemical diversity is a treasure that should not be squandered. One reason to maintain ecosystems such as rain forests intact is that less than 10% of plant species have been systematically investigated for their chemical products. Also, many microbes, insects, and other species have not been explored for useful products.

Discovering which natural product is useful has historically been a slow, laborious effort. Our improved understanding of the molecular basis of life and of disease has allowed us to develop methods for rapid screening of libraries of natural products for compounds that interact with specific molecular targets. Synthetic chemists have used the techniques of combinatorial chemistry to generate large numbers of chemical compounds that also can be screened in a similar manner to identify promising drug candidates. Tremendous advances have been made in our capabilities to rapidly make a wide variety of complex new chemicals for such testing.

Although we do not know the identity of all chemical species in a living cell, we do know many of the most essential components and have determined their molecular structures. Molecular analysis of living cells has led to a flow plan of information in molecular biology, known as the Central Dogma: The information necessary for a cell is encoded in the double helix of DNA. DNA acts as a template for its own replication, and segments of DNA that encode information for the primary structure (i.e., amino acid sequence) in a protein are called genes. The information for production of a protein is first transcribed from DNA through synthesis of a messenger-RNA molecule by the process of transcription, and regulatory elements on the DNA help determine when and how often a particular gene is transcribed. The information on the messenger RNA is converted to a protein through the process known as translation; if the physiological conditions in the cell are correct, the nascent protein folds into its proper three-dimensional shape. Proteins act as catalysts (called enzymes), transporters, receptors of information, regulators, and structural elements in the cell. Their three-dimensional shape is critical to biological activity.

The language of biology uses four letters (A, T, C, and G corresponding to four different nucleotides) in DNA, and three-letter words. Each three-letter word specifies a particular amino acid (or signals to start or stop translation). Other combinations of DNA letters (of various lengths) combine with proteins in the cell to block or encourage transcription of genes; these combinations of letters constitute regulatory elements. The language of biology is universal; the same

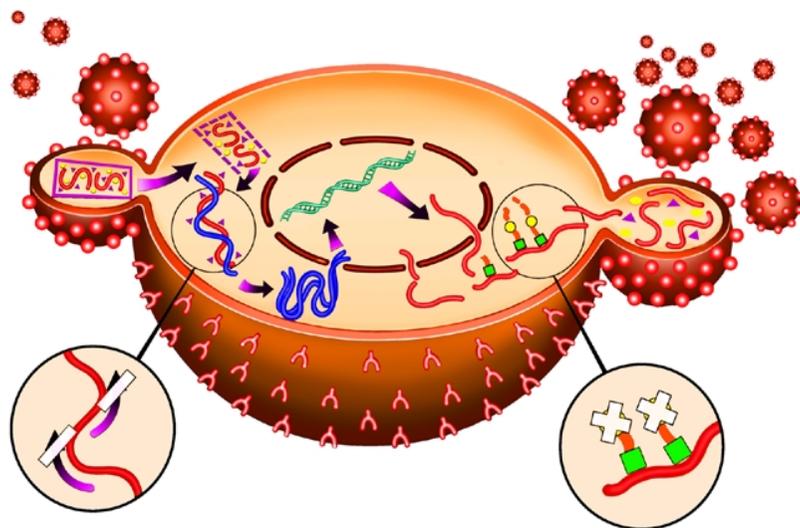
language applies to humans, plants, and microbes. This universality makes genetic engineering and gene therapy feasible.

Recent advances in technology, using modern chemical techniques for structure determination, have allowed us to sequence or read the letters in the DNA, or genome, of a cell. We have genomic sequence data for humans, an insect, a plant, simple multicellular organisms, and many microbes; more are constantly being produced. These sequences represent the total genetic and biochemical blueprint for each of these organisms. This information is useless unless we learn to read it intelligently; that is, to relate linear sequence information to cell and organismal function. Functional genomics is a term used to describe that relationship, and it will be a primary challenge for the next 50 years.

The simple sequence of letters in the genome tells us only a little. The details of three-dimensional structure are important to understanding the chemical processes of life. For example, the discovery that DNA forms a double helix made it clear how genetic information is passed on and utilized. The biological activity of the proteins encoded on the DNA is dependent on their specific three-dimensional structure. Many chemists are concerned with how best to determine the structure of such proteins. Ideally, that structure could be predicted from the sequence of amino acids that correspond to the code in the gene on the DNA. This remains a challenging problem in computational chemistry (Chapter 6), but a combination of experimental and theoretical techniques have advanced our understanding of structure and function in proteins. For example, x-ray methods can be used when a protein can be crystallized (although this is often difficult). Nuclear magnetic resonance (NMR) techniques can be used to probe the structure of proteins in solution. Many of the computational techniques are related to recent advances in sequencing of DNA. Bioinformatics includes computational chemistry with the goals of predicting function and three-dimensional shape directly from the amino acid sequence—by comparison with sequence, function, and structural information for other proteins (often from other organisms).

Knowing protein structure can provide direct benefits to human health. The precise molecular structure of a protein gives it great selectivity in distinguishing among substrates. Sometimes that activity can be blocked by molecules that are similar to the substrate but do not cause a reaction or response when bound to the protein.

For example, with the crystal structure of the aspartyl protease from human immunodeficiency virus (HIV-1) in 1989 came the opportunity to design molecules to block this important enzyme that acts as a molecular scissors. HIV is the virus responsible for AIDS. Essential to viral replication, the HIV protease cuts long strands composed of many proteins into the functional proteins found in mature virus particles. This proteolysis occurs at the very end of the HIV replication cycle (Figure 7-1). The three-dimensional structural information derived from the x-ray crystal structure, combined with computer modeling techniques, allowed chemists to design potent, selective inhibitors of the protease enzyme (Figure



**FIGURE 7-1** The HIV replication cycle. A virus particle (small sphere) attaches to a cell in the immune system such as a lymphocyte (large sphere, shown here in cross section) as the first step. Two complementary approaches to AIDS therapy utilize (a) reverse transcriptase inhibitors (enlargement, lower left) to block incorporation of the viral genome into the host cell, and (b) HIV protease inhibitors (enlargement, lower right) to block cleavage of proteins into key functional enzymes that are required for mature viral particles. Copyright Merck & Co., Inc., Whitehouse Station, New Jersey, USA, All Rights Reserved, used with permission.

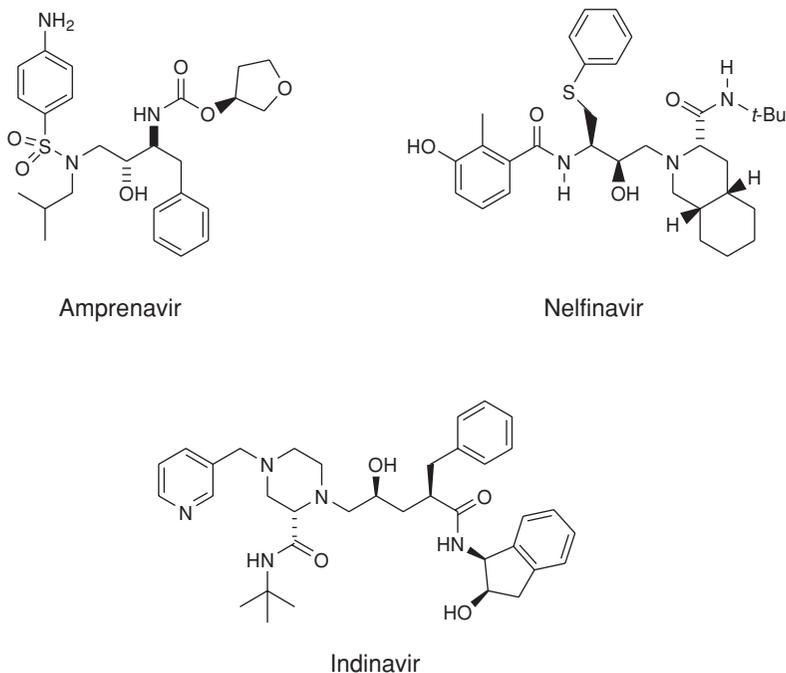
7-2). Design of complex molecules that “dock” into a target is only a first step—the molecules had to be synthesized from simple building blocks. The excellent stereocontrol of reactions like the Jacobsen and Sharpless epoxidations and the Evans aldol reaction was essential to the construction of molecules with as many as five chiral centers (for which  $2^5$  or 32 possible stereoisomeric forms are possible). Target molecules had to be made in pure form and tested, and eventually the single “active” isomer had to be produced with >99.8% purity at a level exceeding 100,000 kg/year. A decade ago, production of synthetic drugs with this level of molecular complexity was inconceivable. Protease inhibitors have become an important part of the treatment for AIDS patients.

A major lesson learned from the first draft of the human genome sequence<sup>2</sup> is that there are fewer genes (perhaps only 30,000) than originally predicted (over

<sup>2</sup>J.-M. Claverie, *Science*, 291, 1255, 2001; J. D. McPherson, et al., *Nature*, 409, 934, 2001; J. C. Venter, et al., *Science*, 291, 1304, 2001.

100,000). This was a surprise to biologists, who had speculated that the number of genes in an organism's genome might scale according to that organism's level of complexity. Instead, some simple worms such as nematodes have nearly as many genes as human beings! Where are the complex functions encoded that are characteristics of higher mammals? One answer seems to be in the post-translational modification of proteins. During or after their biosynthesis, proteins can be modified with myriad added decorations, such as phosphate, sulfate, and acetyl groups; the modified proteins can have vastly different properties compared with those of their unmodified progenitors. Thus a single protein, derived from a single gene, can be transformed into numerous distinct molecular species and thereby amplify the information content of a very concise genome. Comparisons have shown that post-translational modifications are more extensive in higher organisms.

The chemistry of polysaccharides is a major frontier. Their branched and complex nature makes them far more difficult to synthesize than the linear biopolymers, proteins, and nucleic acids. For this reason, automated synthetic methods for polysaccharides were just created in 2001, several decades after com-



**FIGURE 7-2** Examples of HIV protease inhibitors.

parable methods were perfected for the linear biopolymers. There is still a need for improved syntheses of the linkage that connects sugar residues within a polysaccharide chain, the glycosidic bond. At the moment, each specific linkage must be made with different optimal reagents, making a generalized automated synthesis very difficult.

Our increased understanding of the biology of polysaccharides has led to major breakthroughs in medicinal chemistry. The attachment of white blood cells to cells that line the walls of blood vessels is a hallmark of inflammatory conditions such as rheumatoid arthritis, psoriasis, and transplant rejection. Disruption of this cell-cell binding event would stop the inflammation and improve the patient's health. It was discovered that the pathological binding of these two cell types is mediated by noncovalent association of a receptor on the white blood cell, termed L-selectin, with polysaccharide ligands on the blood vessel walls. Soluble versions of that polysaccharide that can bind to the receptors and thus inhibit cell binding are now in clinical trials as anti-inflammatory drugs.

In most cases, the precise functions of polysaccharides are not known; even their primary sequences are very hard to determine using current analytical techniques. Thus, a major challenge is to crack the "carbohydrate code" and determine the structures and functions of all the polysaccharides found on human cells. Terms such as "glycomics" have already been coined to describe such global efforts.

### **Biochemical Engineering**

Biochemical engineering is both an established and an emerging field that is inherently multidisciplinary. It integrates chemical engineering with biology and biochemistry—to participate in biological discovery or to create processes, devices, or therapies.

For example, bioprocess engineering is concerned with the development of manufacturing processes based on living cells or enzymes to make pharmaceuticals, food ingredients, or chemicals. Much of biochemical engineering activity is directed toward human health and forms an important branch of biomedical engineering, particularly in activities such as drug delivery devices, artificial organs, and tissue engineering (e.g., artificial skin for burn victims).

Modern biochemical engineering has become so focused at the molecular and cellular level that the difference between molecular and cellular biology and molecular and cellular engineering can be difficult to discern. Biologists and biochemists want details of mechanisms and have successfully used a reductionist approach in which they strip away all elements except those directly under study. Biochemical engineers typically require a less detailed description of component mechanisms, but they need to understand how the cell's components interact with each other. Thus, biochemical engineers must view the cell or collection of cells as a whole system. It is often this integrative approach that distinguishes bio-

chemical engineers from biologists and biochemists. The integrative or systems perspective of the biochemical engineer complements the traditional reductionist approach of the biologist.

Another distinction between the biochemical engineer and the biologist is that the creation of a process, therapeutic strategy, or device is the ultimate goal of the engineer, while discovery is the primary goal of the biologist. However, the engineer's approach often leads to new discovery, and many biologists participate in creation. Since some properties of systems emerge only when component parts are integrated together, the complete discovery and understanding of living cells will require the integrative approach common in engineering, in addition to reductionist approaches.

Modern biochemical engineering began with the challenge of large-scale production of penicillin by fermentation during World War II. This challenge required the active cooperation of microbiologists, biochemists, and chemical engineers. Today many small-molecule natural products are made from microbes in large (>100,000 L) fermenters followed by a series of separation and purification operations.

Other major early contributions of biochemical engineering have been in the development of the artificial kidney and physiologically based pharmacokinetic models. The artificial kidney has been literally a lifesaver. Pharmacokinetic models divide the body of an animal or human into various compartments that act as bioreactors. These mathematical models have been used very successfully in developing therapeutic strategies for the optimal delivery of chemotherapeutic drugs and in assessing risk from exposure to toxins.

More recent accomplishments include development of bioprocesses for production of high-purity proteins, using genetically engineered cells. This challenge was particularly difficult with respect to the development of large-scale systems for production of therapeutic proteins using *mammalian* cells suspended (or dispersed) in a liquid medium. Examples of some of these products are tissue plasminogen activator used to treat stroke and heart attack patients, erythropoietin to treat anemia resulting from kidney damage or chemotherapy, and granulocyte colony stimulating factor as an adjuvant to chemotherapy and cancer treatment. Another accomplishment has been the development of effective devices for the controlled release of pharmaceuticals and therapeutic proteins. Localized delivery of drugs (for example, in the brain) has been a key to effective treatment of cancers and other ailments.

Commercial production of paclitaxel (better known by the commercial name Taxol), an important anticancer agent, has been accomplished using plant cell tissue cultures, where cells or small aggregates of cells are suspended in a liquid medium. This technological advance could lead to general methodology for the production of plant-based medicinals from rare and difficult-to-grow plant species. Tissue-engineered products such as artificial skin and cartilage have been recently introduced into the market. The need to combine living cells and poly-

mers under the strictest conditions of sterility challenged the ability of the engineers to mass produce and package these products..

The preceding accomplishments are applied in nature, but required tremendous amounts of basic research on mass transfer, interactions of materials with biological components, fluid dynamics, separation processes (especially chromatography and membrane separations), and biochemical kinetics.

Biochemical engineers also have made major contributions to a better understanding of cells, tissues, and organisms. These contributions fall mainly under such categories as metabolic engineering, cellular engineering, and hemodynamics.

Metabolic engineering refers to purposeful genetic manipulation of the biochemical pathways in a cell to produce a new product, to eliminate unwanted reactions, or to increase the amount of a desired product already produced by a cell. The optimal approach to effective metabolic engineering of a cell is essentially quantitative in nature; biochemical engineers have played the major role in the development and application of the appropriate mathematical models (e.g., metabolic control theory). In addition, chemists have developed a better understanding of the modular cellular machinery used to synthesize natural products and have used the techniques of metabolic engineering to harness these modular processes to create novel molecules. An excellent example is recent work to make novel polyketide antibiotics. Biochemical engineers do much of the current experimental work on metabolic engineering in collaboration with other chemical scientists.

Cellular engineering, while closely linked to metabolic engineering, is concerned not so much with metabolic pathways but instead with processes such as cell adhesion, cellular mechanics, signal transduction due to growth factors and hormones, and viral infections. By combining mathematical models of these processes with clever experiments we have far greater insight into these biological mechanisms. Such insight can assist in the design of drug candidates. As an example, both models and experiments show that the intuitive assumption that the most effective inhibitor of a receptor-based process would have the highest binding affinity is wrong. Due to receptor recycling a nonmaximal binding affinity is optimal.

### **Large-Scale Production of Proteins from Recombinant DNA Using Suspensions of Animal Cells**

When recombinant DNA technology was developed in the late 1970s and early 1980s, many thought that all proteins could be produced in easy-to-grow bacterial cultures. This optimism proved incorrect; bacteria were incapable of making some proteins in a therapeutically useful form.

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For these proteins, mammalian cells proved better hosts, as they could process the protein with intracellular machinery similar to that in humans. However, large-scale production of proteins in cell culture was problematic. Mammalian cells had to grow attached to a solid surface, such as glass in “roller bottle” culture. While the Federal Drug Administration (FDA) had approved some processes for vaccine production that used cell cultures, it required that these cells be “normal.” Normal mammalian cells can divide only a few times before they stop growing, making scale-up to large volumes difficult.

The first large-scale process to circumvent these limitations was one developed by Genentech, Inc. (South San Francisco, CA) for production of recombinant tissue plasminogen activator (tPA). This protein dissolves blood clots and can be used to treat heart attacks and strokes. This process was developed in the mid-1980s, resulting in final product licensure in 1987. The process required both regulatory and technical breakthroughs.

Genetic scientists chose to use a Chinese hamster ovary (CHO) cell line as a recombinant for production of human therapeutics. This cell line is “transformed,” which means it can replicate indefinitely. All cancers arise from transformed cells, so Genentech had to convince the FDA that their process, including recovery and purification, would eliminate the possibility of injecting patients with a “transforming factor” that could cause cancer in a patient. In addition, they had to adapt the CHO cells to grow in suspension culture (i.e., cells dispersed in liquid medium and unattached to any surface) and to grow in a medium without serum (which is produced from blood by the removal of cells). Serum-free suspension cultures of CHO cells greatly simplified processing problems and reduced cost. The absence of serum and the contaminating proteins it contained simplified recovery and purification of tPA, and reduced degradation as tPA was secreted from the CHO cells. By using suspensions, and thus being freed from the constraints of surface-to-volume ratios inherent in roller bottle or similar techniques, it was possible to design large (12,000 L) stirred bioreactors that could be readily scaled up and that would maintain high levels of volumetric productivity (mg tPA/L-hr). The bioreactor design issues were complex, as no one before had built a bioreactor that could supply sufficient oxygen and nutrient to the cells in such a large system while stirring gently enough not to damage the cells with high levels of fluid shear. This required novel designs of reactor shape and impeller, based on an understanding of the cellular growth kinetics, mass transfer, and fluid dynamics. The process required development of a novel large-scale, low-shear, tangential flow filtration technology for the rapid, aseptic removal of spent medium from cells.

The success of the project depended on the ability of biochemical engineers, chemists, and life scientists to work together. Success depended on an integrated vision of the process and an understanding of how each component interacted with the other components.

While production processes based on serum-free suspension cultures of CHO cells are now common, the integrated approach to bioprocess development remains essential to success. Chemists and biochemical engineers need sufficient knowledge in the life sciences to interact fruitfully with biologists. The cell remains the “real” bioreactor, but efficient processes required the design of macroscopic bioreactors and operating strategies that effectively couple to our knowledge of the cellular reactors housed in human-designed bioreactors.

Other examples of important insight obtained by biochemical engineers are the effects that physiological values of fluid stress have on cells. Cells that line blood vessels are normally exposed to blood flow. This flow places a mechanical stress on a cell that not only alters cell shape but also its function. The mechanical stresses alter expression of genes. The mechanisms by which this occurs in cells are incompletely understood and a matter of active research.

### **PROGRESS TO DATE**

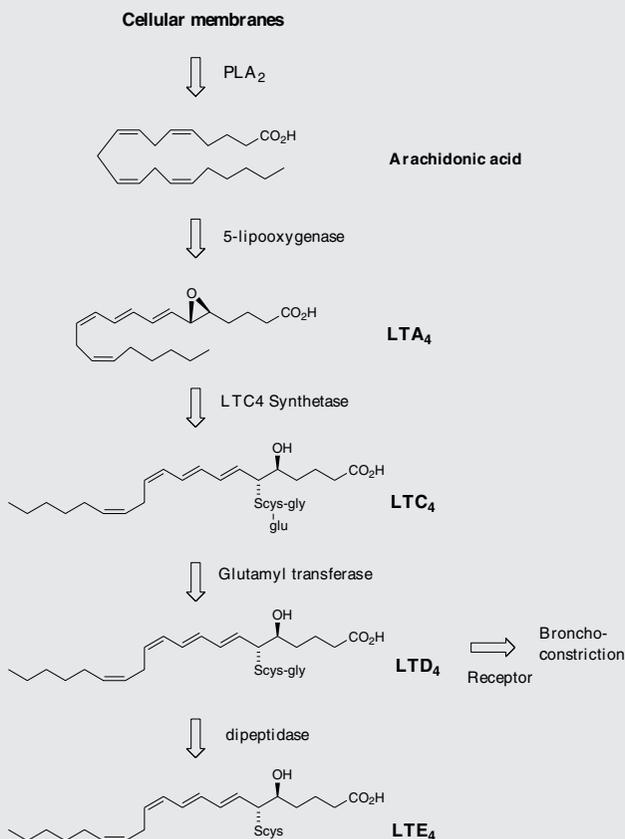
When one looks back at the last decade of the 20th century it is astonishing to see what was achieved in the understanding of life’s machinery. Decoding these mysteries and producing a detailed molecular picture of how things work is a critical step. However, nowhere has the role of chemistry been better illustrated than in the creation and development of new medicines and therapies.

### **Selective Asthma Therapy**

In the 1930s an unknown material was hypothesized that was proposed to cause a slow and sustained contraction of smooth muscle. It was named the “slow reacting substance” (SRS). By 1940 a similar substance was reported to be found in guinea pig lungs and was called the “slow reacting substance of anaphylaxis” (SRS-A). Over the next 40 years, while no one could isolate, characterize, or synthesize this mate-

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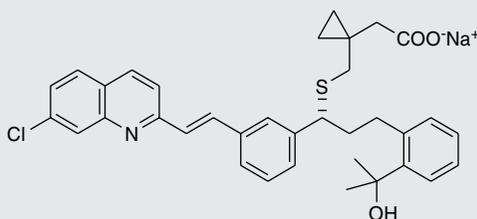
rial, the belief was that SRS-A played a key role in human asthma. In 1979, Bengt Samuelsson proposed a structure for SRS-A that was derived from arachidonic acid and the amino acid cysteine. He called it leukotriene C.



Formation of leukotrienes via the arachidonic acid cascade.

Soon after, the complete structure of SRS-A was finally determined by total synthesis. SRS-A turned out to be a mixture of 3 substances now known as leukotriene C<sub>4</sub> (LTC<sub>4</sub>), leukotriene D<sub>4</sub> (LTD<sub>4</sub>) and leukotriene E<sub>4</sub> (LTE<sub>4</sub>) in which LTD<sub>4</sub> was predominant. The jump from a biological observation in 1938 to a molecular structure of LTD<sub>4</sub> opened the door to a novel and selective treatment for asthma. The theory was that if one

could find a molecule that specifically blocked the action of  $\text{LTD}_4$  on the lung, it would be possible to prevent the tightening of the airways found in asthma. Eighteen years after Samuelsson's proposal, after the synthesis and testing of thousands of man-made compounds, Singulair (montelukast) reached the world's pharmacies. Leukotriene modifiers are recognized to be the first important advance in asthma therapy in 25 years.



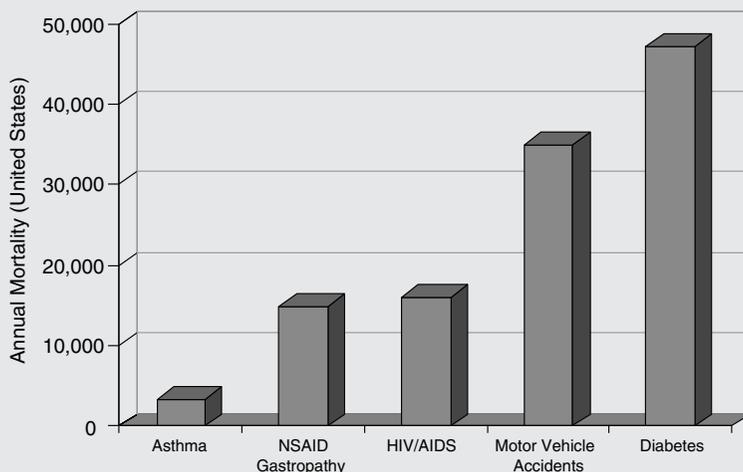
Singulair (montelukast)

This is just one example of how the chemical understanding of one of life's processes at the molecular level resulted in the solution to a 60-year-old problem. The selective  $\text{LTD}_4$  receptor antagonist was specifically designed to take the place of  $\text{LTD}_4$  on smooth muscle. Such approaches—where the drug molecule does only what it's intended to do, without indiscriminately binding to other receptors in the body—are aimed at selective therapies that are free of side effects. It is that selectivity, designing molecules with precision based on structural information, that characterizes the state of the art of chemistry as we enter the next millennium.

Underlying the discovery of a selective asthma therapy are numerous advances in analytical and instrumental techniques as well as synthetic methods that allow the construction of complex molecules. Practical catalytic, stereospecific, and organometallic methods that permit a high level of stereochemical control have enabled production at the multiton level of molecules previously inaccessible even at the gram scale.

## Selectivity and Anti-Inflammatory Drugs

The theme of selectivity—based on detailed understanding of molecular structure and function—underlies most recent therapeutic advances. Sometimes a biochemical “revisiting” of an old discovery enables dramatic improvements in the quality of life. Among the most widely used classes of medicines are the nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin and ibuprofen. Used for years, these pain killers and arthritis treatments work by blocking the effects of arachidonic acid on an enzyme called cyclooxygenase (COX). A major drawback to inhibiting COX is that by doing so you inadvertently block its role in protecting the gastrointestinal tract. The resulting ulcerative gastropathy is responsible for a large number of hospitalizations and deaths. Recently it was discovered that cyclooxygenase is not a single enzyme but rather a family containing at least two nearly identical members: COX-1 and COX-2. While COX-1 is responsible for the good gastroprotective effects (and shouldn't be blocked) COX-2 is the enzyme involved with pain and inflammation (the real target). The COX-2 hypothesis stated that if one could invent a specific COX-2 inhibitor, it would be an effective anti-inflammatory and analgesic medication with substantially reduced gastrointestinal (GI) toxicity compared with the classical NSAID's aspirin and ibuprofen.



Significant mortality is associated with NSAID gastropathy. G. Singh and G. Triadafilopoulos, Epidemiology of NSAID induced gastrointestinal complications, *Journal of Rheumatology*, 1999, 26, 56, 18-24, by permission of Oxford University Press.

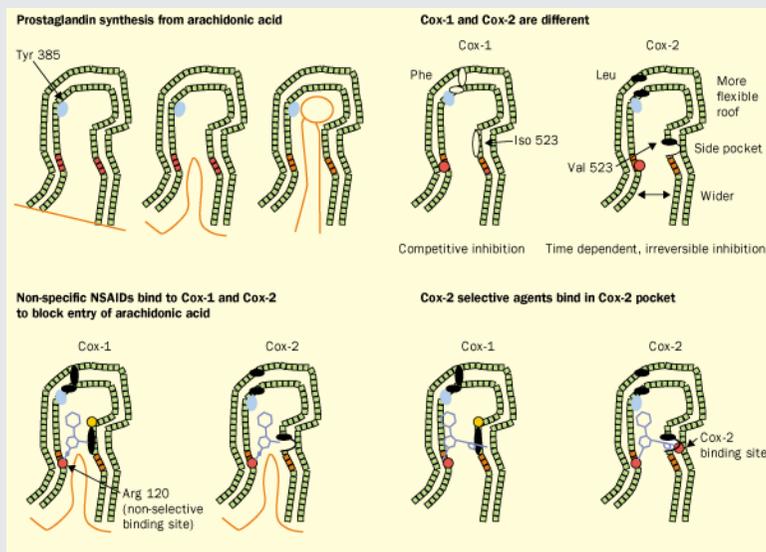
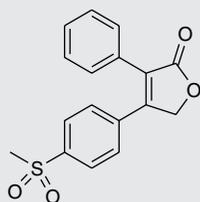
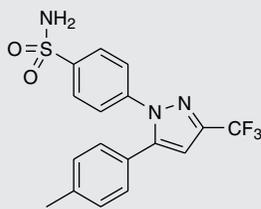


Figure reprinted with permission from Elsevier Science (*The Lancet*, 1999, 353, 307-314).

Again, detailed structural information at a molecular level was the key. Once these “pictures” were available slight chemical differences between the COX-1 and COX-2 isoenzymes could be seen: COX-2 had a side pocket while COX-1 didn’t. This meant that a molecule that could dock into the COX-2 side pocket (binding site) but not into COX-1 would specifically block COX-2 without touching COX-1. In 1999 this hope was realized with the availability of COX-2 selective anti-inflammatories such as Rofecoxib and Celecoxib that can be as much as 50-fold selective for the target.

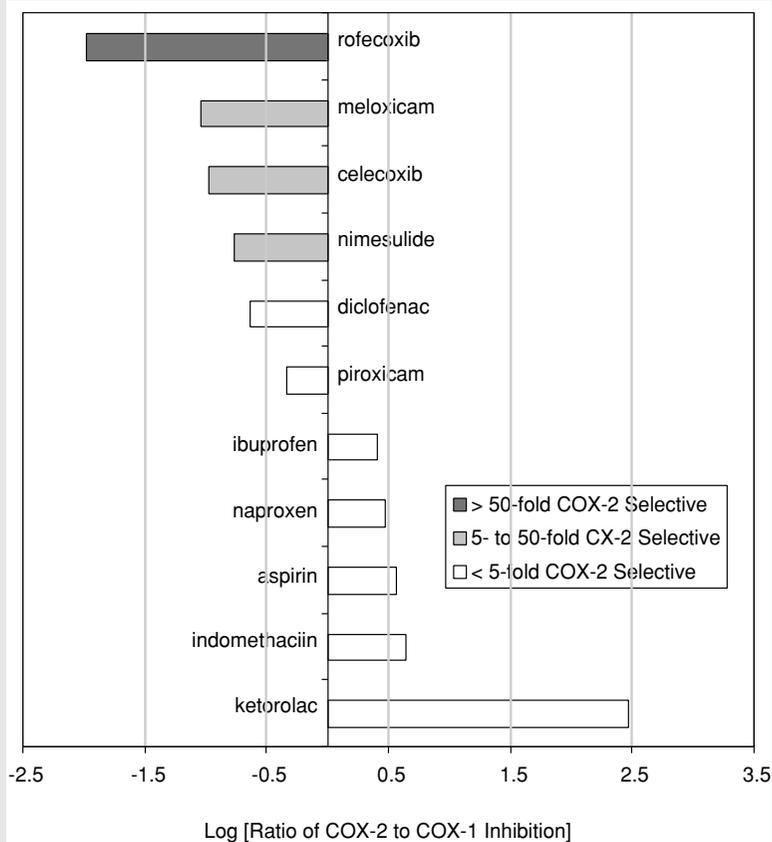


Rofecoxib



Celecoxib

*continues*



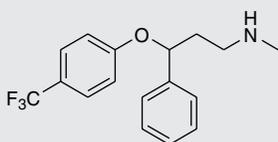
COX-2 selectivity of marketed compounds. Adapted with permission from T.D. Warner et al. *Proceedings of the National Academy of Sciences*, 96, 13, 7563 (1999). Copyright 1999 National Academy of Sciences, U.S.A.

### Specificity and Therapy for the Human Brain

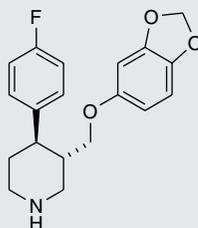
Nowhere is the need for specificity so great as in trying to design therapies for the human brain. Here there are numerous receptors that affect our moods, sleep, alertness, memory, and coordination. Even though the importance of serotonin (5-hydroxytryptamine, 5-HT) had been known to neuroscientists for over 100 years, it wasn't until the discovery of drugs

like Prozac (fluoxetine hydrochloride) and Paxil (paroxetine hydrochloride) that selective antidepressive drugs became available. The antidepressive effect results from inhibition of serotonin uptake by neurons in the brain, thus ensuring that circulating levels are adequate. The selectivity results from selective binding compared with older drugs (tricyclics) that were less discriminating in their binding to other brain receptors. The net result is fewer side effects. As the molecular basis of memory and behavior become clearer, we will see a leap in the effectiveness and specificity of drugs for the central nervous system.

The arrival of the year 2000 coincided with a milestone in modern science; many believe that deciphering the human genome will provide a road map for therapeutic intervention. We are already seeing medicines that act not directly on a target tissue but on receptors that regulate the transcription of genes. The ability to “tune” the molecular signaling that continually occurs in our bodies will eventually allow for more exquisite control of the cellular processes of life. If today’s chemistry lets us turn things on or off by blocking or unblocking receptors and enzymes, tomorrow’s molecules will be able to balance complex metabolic processes like growth and aging by fine tuning the regulation of genes and their products.



Prozac



Paxil

## CHALLENGES AND OPPORTUNITIES FOR THE FUTURE

The opportunities for discovery and invention at the interface of chemistry, engineering, and biology are enormous, and many examples have been described in the preceding sections. This interface represents a true research frontier—one that is critical to our ability to develop new chemistry for the prevention, diagnosis, and treatment of human disease. The continuing challenge is to discover the chemical identity of all the molecules that make up living organisms and the way they bind to each other and organize into biological structure—membranes and cell structures such as nuclei, ribosomes, etc.

## Ribosomes

The nucleotide sequences of the genes encoded in DNA are transcribed into the same sequences of messenger RNA, again carrying the genetic code, and these RNAs direct the synthesis of proteins with defined sequences of amino acids. Protein synthesis occurs in a cellular machine called a ribosome, which takes in messenger RNA and some amino acids linked to transfer RNA and uses base pairing to direct their assembly into a protein. The base pairing occurs because each kind of amino acid is attached to a different transfer RNA, one that carries a code for that particular amino acid. Thus messenger RNA plays the role of template for protein synthesis, and transfer RNA guides the amino acids to the correct spot. Assembling the protein still requires a catalyst to link the amino acids together.

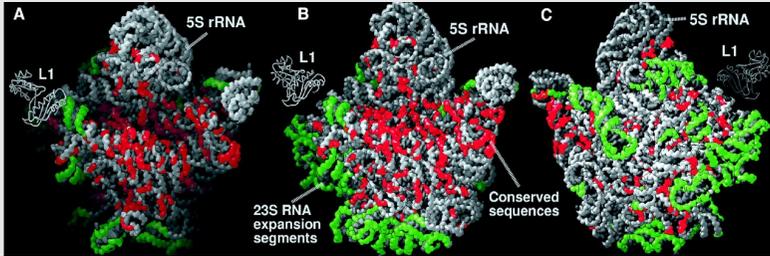
Essentially all biological catalysts in the modern world are themselves proteins, enzymes. However, in 1989 Sidney Altman and Thomas Cech received the Nobel prize in chemistry for showing that RNA itself could act as a catalyst for some biological reactions. This led to the idea that in an earlier time, as life was evolving, RNA may have been both the information molecule (a role usually played by the more stable DNA now) and the catalyst (the role that protein enzymes now play.) Since this idea indicates that in early times the synthesis of proteins was catalyzed by RNA, not by protein enzymes, the intriguing question is whether this is still true today.

Ribosomes are complex structures consisting of one small RNA molecule and two large ones together with some 50 to 60 different proteins. Their general shape had been determined by electron microscopy some years ago, but a major breakthrough occurred in 2000. X-ray diffraction was used to determine the detailed molecular structure of a ribosomal particle that consists of almost all the molecules in a ribosome and exhibits the full catalytic and regulatory functions of a ribosome.<sup>3</sup> The trick was to get this large particle, about 100 times as large as a simple protein enzyme, to crystallize so the x-ray technique could be applied. The results are striking, but for the real details it is important to consult the original articles). Such a detailed structure can help medicinal chemists to develop useful drugs that bind to the ribosome, but the more important result has to do with the catalytic center.

The catalytic center of the ribosome, where the protein is actually made, is now seen to consist of RNA, not of a protein enzyme! The many

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<sup>3</sup>N. Ban, P. Nissen, J. Hansen, P. B. Moore, and T. A. Steitz, *Science*, 289, 905, 2000; P. Nissen, J. Hansen, N. Ban, P. B. Moore, and T. A. Steitz, *Science*, 289, 920, 2000.



The large ribosomal subunit at 2.4 Å resolution. (A) The particle rotated with respect to the crown view so that its active site cleft can be seen. (B) The crown view. (C) The back view of the particle, i.e., the crown view rotated 180° about its vertical axis. Reprinted with permission from Ban et al., *Science* 289, 905 (2000). Copyright 2000 American Association for the Advancement of Science.

proteins present help organize the structure, but they do not play a catalytic role. This is in line with the idea that the original process in early life forms used RNA alone. As proteins were created in processes guided and catalyzed by RNA, some proteins were incorporated into the RNA catalytic unit during evolution and improved the ribosome's function. A follow-up paper<sup>4</sup> indicates a way in which the RNA could carry out the catalyzed synthesis of proteins. A particular adenosine unit in the catalytic RNA has the correct properties to be able to assist the formation of peptide bonds, which are the links in proteins.

All this is basic chemical research that has wide importance, determining the molecular structure of a component of living cells. Simply, it tells us the details of how proteins are now made, but more generally it strengthens the picture of how life may have started in a world where RNA was both information molecule and catalyst. It is a major advance in scientific understanding.

<sup>4</sup>G. W. Muth, L. Ortoleva-Donnelly, and S. A. Strobel, *Science*, 289, 947, 2000.

One driver for new discovery will be the completion of the human genome project. As a result of this project, the locations and sequences associated with the tens of thousands of genes of the human genome will have been determined. In the post-genomic era, then, we will know the DNA sequences and genes of a human being, but that is only the start. What are the functions associated with these sequences? We will need to isolate the proteins that are the gene products,

determine their structures, characterize their reactions and their partners in reactivity. To perturb the actions of these proteins, we will need to develop diverse arrays of small-molecule inhibitors and activators. While the human genome project gives us access to the library of the cell, we will need to learn much to exploit the information that we will have.

For example, although we designate gene sequences by a one-dimensional string of letters, the protein gene products they encode have three-dimensional architectures, and when properly folded they carry out biological function. A critical challenge in this post-genomic era will be to make the connections between protein sequence and architecture, and between protein architecture and function. We need to learn to predict how a protein folds and the relationships between a folded structure of a protein and its function. Indeed, in reaching that level of chemical understanding, we can then seek to design new functions for proteins. Both combinatorial and rational design strategies may be applied in the construction of novel biologically based catalysts.

Genomics and gene arrays will become increasingly important in strategies to prevent disease. Today, for example, we make use of simple assays such as the PSA (prostate screening antigen) test in the early detection of prostate cancer. Transcriptional profiling using gene chip technology will likely facilitate analogous tests for all cancers by simultaneously measuring all relevant mRNA levels. We will be able to determine what mRNAs or small natural products rise in concentration in association with cancers, and hence use detection methods for these molecules in cancer prevention. A challenge resulting from the enormous amount of information associated with such transcriptional profiling will be the determination of causal relationships, and of the partners and pathways associated with cellular transformation. Indeed, a major intellectual challenge to the chemical sciences is developing a systematic framework and computational tools to relate microarray data, as well as data on protein levels, to a description of the dynamic regulatory networks controlling cellular functions.

Proteomics is a combination of experimental and analytical tools to determine the total protein content of a cell or tissue. While genomics identifies the potential proteins in an organism, proteomics provides information on which proteins are actually present in a tissue under specific environmental conditions and accounts for the physiologic history of the tissue. Proteomic information is difficult to obtain due to the large amount of chemical heterogeneity displayed by proteins and our inability to amplify the amount of proteins in a sample. In contrast, polymers of nucleic acids are rather more chemically homogeneous and can be amplified using the chemical technique of polymerase chain reaction (PCR). Currently much proteomics work is accomplished using a technique called two-dimensional gel electrophoresis. This technique is slow, requires highly skilled technicians, and many proteins in a cell are too rare or too hydrophobic (water hating) to be resolved by this technique. Nonetheless, 2-D gel electrophoresis has been used successfully to monitor prion diseases (e.g., mad cow disease) and

shows promise in the diagnosis of neurodegenerative disorders such as Alzheimer's disease. A major opportunity in the chemical sciences is the development of microarray technologies that can provide more rapid and complete proteomic information. The techniques of biotechnology applied on the nanoscale may result in miniature devices that can be used in a massively parallel fashion to do rapid separation and analysis of DNA, RNAs, or protein solutions.

Progress in genomics and proteomics offers opportunities also in the diagnosis and treatment of disease. We will soon be able to develop the chemistry necessary to routinely detect genetic variations in individuals, and to do so for a full range of genes. In fact, some pharmaceuticals that are largely effective and might represent medical advances currently fail during clinical trials as a result of an adverse reaction within a genetic subpopulation. With genetic screening, and a better understanding of the underlying biochemistry, we will be able to tailor-make therapies for patients based on their genetic dispositions.

More generally, as described earlier, medicinal chemistry has greatly contributed to the fight against disease, but there are still major challenges ahead. For example, we don't yet have generally effective drugs to treat viral diseases, such as influenza or Ebola (although some trials of a new drug for the treatment of influenza indicate that it decreases the length of the infection). This is critical. Imagine the problem if the HIV virus that causes AIDS, or the Ebola virus that kills quickly, were able to be transmitted by the bite of a mosquito, as some other less lethal viruses can be. Until we have effective medicines to cure such viral infections, humanity is at great risk.

Another problem is bacterial resistance to antibiotics. As doctors have treated people with the available antibiotics that medicinal chemistry devised in the past, they have selected for strains of bacteria that are resistant to those antibiotics. There is now a race against time by medicinal chemists to devise new antibiotics that will work against the resistant organisms. If we do not succeed, many bacterial infections that we thought had been cured will emerge again as major threats to our health and life.

We still need much better medicines to cure cancer, heart disease, stroke, and Alzheimer's disease. We need better drugs to deal with obesity, diabetes, arthritis, and schizophrenia. The treatments of diabetes, arthritis, and mental defects such as schizophrenia or manic depression are not yet cures, just ways to keep the symptoms under control. Cures are needed. Insights from genetics may help guide us toward elegant and rational cures, but we will also make use of screens to identify natural products and libraries of randomly generated synthetic compounds (combinatorial chemistry). A semi-empirical approach may be the best hope over the next two decades to yield drugs to alleviate these diseases.

Many of the natural products may come from "unusual" organisms and may be difficult to synthesize. In those cases, it will be necessary to develop appropriate bioprocesses to produce, recover, and purify these compounds. Both chemists and biochemical engineers will be involved in creating such processes.

But medicinal chemistry will also change in basic ways. Indeed, we are entering a completely new era of **molecular medicine**. We will develop technologies to screen the effects of small molecules on large arrays of gene products, from enzymes to receptors, and doing so will require advances in fields ranging from biochemistry to material design. We will develop the tools to create genomic maps of protein-protein contacts and chemical tools to decipher the hierarchy of those contacts. Our ability to digest and exploit the enormous information we obtain will also provide challenges in computation, in structure prediction, and in our quantitative understanding of molecular recognition. As a result, fundamentally new strategies will be developed to attack disease on a molecular level. For example, it is already clear that strategies to fight cancer are shifting, from those centered on maximizing toxicity in cancerous cells to those where we activate or harness different signaling pathways of the cell, depending on whether the cell has undergone transformation from normal to cancerous.

Among the fundamental new strategies, and certainly an important step to be taken by chemists in this new era of molecular medicine, will be developing a general understanding of how small molecules can be utilized to regulate gene expression and signal transduction. The goal is the design of small molecules not simply as general poisons to the cell or to some cellular function, but instead as reagents that turn off or turn on critical pathways. This challenge depends upon advances also in our understanding of **molecular recognition**. When a protein or small molecule binds to a particular receptor, an ensemble of weak noncovalent contacts are specifically arrayed in three-dimensional space to facilitate this recognition of one molecule by another. Chemists are now working on general strategies to achieve highly specific molecular recognition, and doing so is a first step in the rational design of new drugs as regulators of cellular processes.

Associated with this question is how to target these small molecules to sites of specific action in the cell or tissue. We have, for example, made substantial progress in delineating how some small molecules and metal ions are trafficked through the cell. Can we apply this knowledge to invent strategies for targeting small molecules to specific organelles within the cell? Our current understanding of what controls cell permeability and bioavailability is primitive, often not appreciably more advanced than “oil versus water.” As we develop a molecular perspective concerning the trafficking of molecules into and through the cell—as well as the chemistry underlying what distinguishes the surfaces of different cells—we will establish a more rational approach to targeting molecules more powerfully, and even with tissue specificity.

Because cells and the body respond not only to genetic information but also to environmental cues, any analysis must take into account the time and environment-dependent nature of the biological system. Because of their training in analysis of integrated systems, biochemical engineers should be able to contribute integrated, quantitative models of these biological systems to guide the selection of targets for intervention and the synthesis of a precise delivery system. In some

cases these devices will need to be “smart” devices to respond to a current physiological state. An example of such a device, already in research and development, is one to monitor blood glucose levels and to release insulin in response to changes in blood glucose level. This device would effectively mimic the responses of the natural pancreas. Other delivery systems may mimic viruses for DNA delivery to specific target cells as a more controllable method for gene therapy. Indeed, the controlled delivery of macromolecular therapeutics with temporal and spatial control of therapeutic distribution is an important goal for chemists and chemical engineers.

### **Controlled Delivery of Therapeutics**

Many pharmaceuticals are designed to effect change in a single organ or tissue. Traditional methods of drug delivery using pills or injections require the pharmaceutical to enter the blood stream and to be dispersed throughout the body (systemic delivery). Often undesirable side effects occur in nontarget organs before a therapeutically useful level of the agent is achieved at the target organ or tissue. Alternative methods of drug delivery are needed to deliver the drug to the right tissue, at the right time, and at the right amount.

As an example, consider treatment of a brain tumor. The brain protects itself from the entry of potentially toxic substances through a blood-brain barrier, which is a highly organized cellular barrier to the transport of such compounds from the blood into the brain. To administer a chemotherapeutic agent to the brain through injection into the blood stream may be impractical since a very high concentration of the drug may be necessary for the drug to cross the blood-brain barrier, and the side effects of the drug on other organs in the body may be toxic. Robert Langer developed a solution to this problem and related ones through the construction of polymeric devices to release drugs at a predetermined rate for extended periods. In this particular disease, the brain tumor is removed and polymeric disks filled with a chemotherapeutic drug are inserted. The polymers have been carefully synthesized to be biocompatible and to break down at a known rate in bodily fluids. As the polymer matrix is dissolved, the drug is released slowly at high local concentrations for many weeks, killing residual cancer cells. Since the polymer disks are in the brain, the drug does not have to diffuse across the blood-brain barrier. Thus, the target, the brain, receives a high dose of drug in the area near the tumor, and the rest of the body experiences only low levels of the drug. This therapy is currently in use and can significantly extend the symptom-free lives of patients.

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Langer received the Draper Prize from the National Academy of Engineering in 2002 in recognition of his work on development of modern biomaterials. The polymer used for controlled release of chemotherapeutic agents in the brain is only one example. Other examples include the use of such biomaterials for controlled release of large molecules (proteins or DNA for gene therapy), as scaffolds for tissue engineering where they release growth-promoting signals, and porous aerosol particles for inhalation drug delivery. The controlled-release drug delivery industry is estimated to have revenues of \$20 billion a year with excellent prospects for continued growth. This industry is based on combining a knowledge of polymer synthesis, polymer interaction with biological molecules, the kinetics of the reaction of specific chemical bonds in the polymer with water or biological fluids, and the rate of mass transfer of molecules in a polymer matrix and in tissue.

We will also look to the chemical details of biology for lessons in how to carry out complex and important reactions under mild conditions. Today, the chemical industry produces ammonia from nitrogen through a high-temperature, high-pressure reaction that consumes lots of energy, yet microorganisms are capable of carrying out the same reaction at normal pressures and temperatures within the environment of the cell, using a metalloprotein catalyst called nitrogenase. Structural insights into this and other remarkable metalloprotein catalysts have recently become available. But can we now harness that understanding to develop new methods and new small molecular catalysts that incorporate the key attributes of the natural enzymes? Many of these enzymes, nitrogenase in particular, are capable of activating small, abundant, basically inert molecules through multielectron reactions. A tremendous challenge to the chemist lies in the design and application of catalysts, whether small molecules or materials, that can carry out such multielectron transfers to activate small molecules such as nitrogen, oxygen, and methane. Imitating some aspects of life, **biomimetic** chemistry is not the only way to invent new things, but it is one of the ways.

We will look to chemical biology for guidance not only in designing new smaller catalysts but also in devising methods to assemble large molecular machines. Replication, transcription, and translation, as well as other critical cellular functions, appear to be carried out through the function of multiprotein/nucleic acid particles. Advances in x-ray crystallography coupled with other imaging methods such as NMR and electron microscopy are now providing our first snapshots of these macromolecular machines, such as the ribosome in which proteins are synthesized in the cell. A spectacular recent advance is the determination of

the three-dimensional chemical structure of the multimolecular photosynthetic reaction center, for which Johann Deisenhofer, Robert Huber, and Hartmut Michel received the Nobel prize in 1988. New advances in imaging will be needed to delineate these and still larger macromolecular assemblies at atomic resolution. These structural pictures provide a critical foundation for understanding how they function. But how do these machines assemble? Are they remarkable examples of spontaneous supramolecular assembly or are they guided in some way in coming together? How do the parts of these assemblies function in concert? Are macromolecular assemblies of such complexity required to carry out these functions? Indeed, can we next begin to design novel macromolecular machines to carry out new, still more complex functions? The construction and assembly of such machines would represent the first step in compartmentalizing chemical reactions. As such, it would represent the very first steps in a tremendous challenge to the chemist and chemical engineer, the design of a synthetic cell.

### Sequencing the Human Genome

The year 2000 marked the completion of the Human Genome Project's primary goal. Through intensive efforts of both private and public agencies, the sequence for the three billion base pairs that encodes the instructions for being human has now been determined.<sup>5</sup> As a result of the Human Genome Project, we have determined the complete chemical structure, nucleotide by nucleotide, of the DNA within each of these chromosomes, the chemical structures that encode our lives. It is an extraordinary accomplishment in chemistry.

Completing this sequencing of the human genome could only be accomplished by building upon discoveries in chemistry made over the past 30 years. It was about 20 years ago that W. Gilbert and F. Sanger showed that small segments of DNA could be sequenced directly using chemical methods. About 10 years ago, instrumentation for automated sequencing was engineered. And building upon all the advances in biotechnology of the last decades, from oligonucleotide synthesis to the polymerase chain reaction and shot-gun sequencing, biochemists in the last 2 years have been able to increase the pace of analysis, so that full genomic maps can be deciphered in months.

In this post-genomic era, what can we expect? Mapping the human genome brings not only a high-resolution picture of the DNA within our

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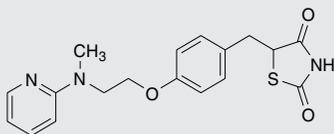
<sup>5</sup>J. D. McPherson, et al., *Nature*, 409, 934, 2001; J. C. Venter, et al., *Science*, 291, 1304, 2001.

cells but also the promise of molecular-based diagnosis and treatment of disease. Therapeutics could be tailor-made to take into account our individual genetic propensities. The cost of such pharmaceuticals will surely decline as clinical trials take such genetic information into account. And preventive medicine will certainly flourish as we begin to catalogue and diagnose our individual genetic predispositions to disease. But none of this is likely to happen tomorrow or even next year. There are many more conceptual advances in the chemistry of life that we need to achieve. At the start of the 21st century, we may know the sequence of bases of the human genome, but we can't yet read this sequence to know what reactions, what chemical functions, actually make us human.

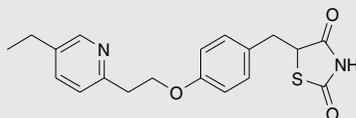
### Post-Genomic Therapies

We have already had a glimpse into the future with the recent approval of a new approach for the treatment of adult onset, noninsulin dependent diabetes (NIDD). In this disease, also known as Type 2 diabetes, the body becomes increasingly resistant to insulin and loses its ability to control sugar levels.

The glitazone family of drugs acts to increase insulin sensitivity and thus increase glycemic control. They do this by acting upstream of a *gene*! As selective activators (agonists) of a nuclear receptor called PPAR-gamma (found in key tissues like fat and liver) they regulate transcription of the insulin responsive genes involved in the control of glucose production, transport, and utilization. Using the cell's signaling machinery, the drugs help the body compensate by getting the cells back to where they should be: sensitive to insulin.



Rosiglitazone



Pioglitazone

The explosive growth in our understanding of the chemical basis of life and its processes couldn't come at a better time. The demographic shift of an aging generation of baby boomers will sorely challenge the nation's resources (both financial and human capital). The need for more effective and cost-efficient therapies will become paramount. As our understanding of the chemistry of the brain grows, intervention will be based on new insights at the molecular level. Selective therapies for problems of memory and cognition, vision and hearing, pain, addiction, and sleep disorders will be designed. The subtle control needed to balance metabolic processes—like weight gain or loss and even aging—is already on the horizon. At the same time the revolution in microprocessors, telecommunications, and materials will enable the production of human “spare parts”: joints and valves, eyes and ears linked to the brain. Even implantable endocrine systems—miniature chemical factories that combine real-time analysis with the synthesis or release of therapeutic agents—are becoming a reality.

### WHY ALL THIS IS IMPORTANT

What are the details of all the chemical transformations that occur in a living cell? How are these details affected by the physical organization of the cell, with various components such as membranes and ribosomes. How do these details differ among cells of different types (liver versus brain, human versus bacterial)? We can also begin to ask what chemical signals direct the development of a single fertilized egg into the different organized tissues in a human being, and how such signals work. What is the chemistry of aging? What special chemistry operates in the brain to store memories? Underlying these functions—functions that make humans what they are—are chemical processes that remain to be discovered and harnessed.

Other opportunities will drive both basic discovery and invention. New and improved drugs will be needed to fight disease and improve quality of life. At the same time, better methods will be needed for delivery of these drugs, and a variety of new medical devices will depend on the work of chemists and chemical engineers. While the engineering of tissue constructs has had commercial success, highly perfused or vascularized tissue remains problematic. Artificial organs, such as an artificial liver, remain objects of intense research. Commercially viable replacement organs are certainly more than a decade away. The primary challenges are understanding the signals that tissues need to control proliferation and differentiation and constructing bioreactors and scaffolds that will provide signals in appropriate sequences.

A closely related challenge is the design of materials that interact with cells or living tissues to promote desired biological responses. Such responses might be cell attachment, cellular differentiation and organization into functional tissue, or promotion of in-growth of bone into an artificial prosthesis such as an artificial hip.

The coupling of the techniques of microfabrication on silicon with cells or biological molecules also offers great promise. Devices at the natural length scales of biological systems will facilitate the use of biosensors that can be implanted. They will also aid the development of models having biological components that can be used to gain predictive insight into *in vivo* systems. Such nanoscale devices may mimic the biochemical interactions in the body by connecting “tissue” compartments in ways that mimic the body’s circulatory system. A particular model that would be useful would be of the blood-brain barrier, to predict which drugs or chemicals may enter the brain.

While we have very functional processes for manufacture of therapeutics, there are significant challenges left to the process chemical sciences. The United States faces a near-term crisis in the production of therapeutic proteins from mammalian cell culture due to the absence of sufficient facilities. Mammalian cell culture is both expensive and has low yields; it is used to ensure that all of the post-translational protein-processing steps (e.g., glycosylation or specific addition of certain sugar complexes to predetermined sites on the protein) are humanlike. Can we find ways to alter cellular machinery in other, more productive host cells, to produce large amounts of proteins with humanlike post-translational processing? Another challenge comes from the need to respond to bioterrorism (Chapter 11). We need new methods to produce large amounts of protective antibodies or vaccines in a matter of weeks rather than years. In addition, ways are needed to integrate better genomic, proteomic, and advanced computational methods with metabolic engineering to inexpensively produce large amounts of non-protein products.

This listing of challenges for the future is not exhaustive, but it should provide the reader with a sense of vast possibilities for the interface of the chemical sciences and engineering with biology. These are complex scientific problems requiring multidisciplinary research. Research at the interfaces of many disciplines requires greater understanding of neighboring fields. We are left with a training paradox—we need highly skilled specialists who are also generalists. In addition, we have a funding paradox—success requires support of both fundamental research and cross-disciplinary research. With collaborative efforts these paradoxes will disappear, and we will realize the incredible potential that lies before us. The early part of the 21st century will be known as the Golden Age of the Chemistry of Life.

## Materials by Design<sup>1</sup>

### **Some Challenges for Chemists and Chemical Engineers**

- Invent improved structural materials that are stable at high temperatures and easily machined.
- Invent materials with useful electrical and optical properties, including high-temperature superconductivity.
- Invent materials that are lighter, stronger, and more easily recycled.
- Invent materials for surface protection (paints and coatings) that are truly long-lasting and rugged.
- Understand and utilize the properties of nanoscale materials and materials that are not homogeneous.
- Build materials with the kind of actuating response found in physiological systems such as muscle.
- Develop and process materials in which complex structural assembly occurs spontaneously or with minimal guidance and in useful time-scales to produce durable systems with diverse utility.
- Create nanomaterials technology from nanoscale chemical science.

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<sup>1</sup>As part of the overall project on Challenges for the Chemical Sciences in the 21st Century, a workshop on Materials and Manufacturing will lead to a separate report. The reader is urged to consult that report for further information.

## GOALS

A material is defined as “the substance or substances out of which a thing is made or composed.”<sup>2</sup> Understanding materials therefore necessitates a marriage between understanding *substances* and knowing how to assemble them into useful *structures*. Materials with specially tailored properties are at the core of nearly all interesting assemblies that are not living, and many that are. Chemical scientists synthesize, characterize, produce, and construct with materials. Moreover, they do this at length scales from molecules at the nanometer level, to polymers and electronic devices at the submicron scale, and to ceramics and cement in large-scale structures. Revolutionary developments are being made in all aspects of materials science. The materials sector of the chemical sciences is vital, both fundamentally and pragmatically, for all areas of science and technology—as well as for the societal needs in energy, transportation, national defense, and medicine.

The overall goal of materials research within the chemical sciences is to explore, design, and control—through synthesis and processing—the relationships among structure, properties, composition, and processing that determine the useful behavior of all materials. The chemical sciences are especially powerful (as they are in all areas of synthesis and manufacturing) in molecular-level construction of material structures. Though the domain of materials chemistry is rapidly expanding, it remains underdeveloped.

A frontier challenge in the chemical sciences is to investigate the chemistry and properties of single isolated molecules and compare that behavior with the average molecular behavior in an assembly, solution, or condensed phase of molecules. Many parts of the chemical sciences are concerned with the collective properties of materials in condensed phases, which have a variety of intriguing and controllable properties. Today, we recognize fully that the most interesting materials are *functional* systems, derived from our evolving knowledge of structure-function relationships. Catalysts are superb examples of chemically functional materials, and the area of catalytic materials is an exemplary branch of modern functional materials science. Responsive materials, often consisting of softer materials, give rise to many kinds of functionality, such as sensing and actuation.

Composites are an important class of solid materials, whose history goes back to ancient times. For example, bricks made only of clay were not as strong as those in which straw was mixed with the clay. Now we use clay as the filler in new polymeric composites to enhance their mechanical properties. The ionic con-

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<sup>2</sup>Random House Webster's Unabridged Dictionary, V2.2 for 16-bit Windows systems, copyright 1999, Random House, Inc.

ductivity of the polymer electrolytes used in energy storage systems also can be enhanced by addition of tiny clay particles. Another example is found in building construction, where concrete is reinforced with steel rods to producing a composite in which the components mutually reinforce the overall strength. Other recent examples are the graphitic materials used in tennis rackets and golf clubs, where long strands of carbon fibers are combined with resins. The science of the boundaries or interfaces between phases, and aggregates of matter with sizes between the molecular and the macroscopic, has become a vigorous part of the chemical sciences. Constructing nano- and microstructures of any complexity requires joint modules or elements through interfaces.

The goals of molecular understanding, synthetic control, and novel fabrication of various materials are inherently based in the chemical sciences and technology. The goal of applied chemistry and chemical engineering is to convert available substances into useful materials, normally by changing their molecular composition and arrangement, through controlled synthesis, processing, and manufacturing methods.

Chemical scientists seek to understand the properties of materials in which there is organization of the components. *Chemistry is the original synthetic nanotechnology (as biology is the original natural nanotechnology); chemists have been designing and executing constructions requiring placements of atoms with subnanometer precision for most of the last century.* Chemical engineers are now aiming to do this on larger scales. As self-assembly and nanotechnology move from laboratory demonstrations to more widespread means of fabrication and manufacturing, the variety of materials available to technology and society will grow enormously. New catalytic chemistry and processes, such as the revolution in metallocene catalysts, is an area where chemists and chemical engineers are creating new routes to macromolecular structural control at the nanometer scale.

Methodologies of synthetic chemistry (Chapter 3) must be adapted to achieve the full potential of chemical materials science and technology. This in turn will allow chemists and chemical engineers to characterize the synthesis of supramolecular entities and the three-dimensional character of materials. Our abilities to achieve these goals in new materials synthesis are enhanced by intricate optical, micromechanical, and spectroscopic probes, just as they are by the use of noncovalent bonding, self-assembly, and assembly directed by forces such as fluid mechanical or electric fields. The miniaturization and diversification of synthesis through biological or combinatorial approaches provide unprecedented opportunities. Chemical science should take better and broader advantage of naturally abundant substances to produce building blocks for molecular (or larger) assemblies. Surface science applied to materials—particularly to organic materials—is of growing importance and will expand significantly with the development of new materials for biotechnology, medicine, information technology, and nanotechnology.

To achieve these goals will require, among many other things, a dramatic increase in the interactions among chemists, engineers, biologists, and physicists.

## PROGRESS TO DATE

Since early civilization humans have been interested in the properties of the various minerals found in the earth. The discovery that materials we now recognize as iron oxides could be heated with charcoal to produce iron led to wonderful new tools in the Iron Age, while similar transformation of other minerals led to copper, tin, and other metals. Although we think of them as common, few metals are naturally occurring; they are produced by chemical reactions of their naturally occurring compounds. One of the earliest synthetic materials is glass, produced over 5,000 years ago by heating various natural minerals together. Clearly, the discovery, refinement, and creation of materials has arisen from the chemical sciences and processing technology (and sometimes vice versa).

### Synthetic Polymers and Self-Assembly

The story of polymers is one that shows enormous effects on human life. Though polymer science revolutionized 20th century life and is now a well-developed academic field, polymer synthesis is still progressing rapidly. Synthetic polymers have often consisted of long chains of identical subunits. Sometimes the synthetic polymer chains have cross-links between the chains (in proteins, cross-links within a chain help determine a specific folded geometry). For many years, copolymers have also been produced to gain the beneficial properties from more than one monomer. Glassy polymers can be blended with rubbery ones to generate desirable mechanical properties. Block copolymers—produced with long runs of one or the other monomer—phase separate on a nanoscopic scale (typically 10 to 50 nm) that is determined by the block molecular weight. These microphase-separated polymers often have remarkably better properties than blends of the two components, and are an early example of using self-assembly to produce new materials.

The architecture of macromolecules is another important synthetic variable. New materials with controlled branching sequences or stereoregularity provide tremendous opportunity for development. New polymerization catalysts and initiators for controlled free-radical polymerization are driving many new materials design, synthesis, and production capabilities. Combined with state-of-the-art characterization by probe microscopy, radiation scattering, and spectroscopy, the field of polymer science is poised for explosive development of novel and important materials. New classes of nonlinear structured polymeric materials have been invented, such as dendrimers. These structures have regularly spaced branch points beginning from a central point—like branches from a tree trunk. New struc-

tures create new possibilities for applications, a direction that will continue to drive materials chemistry.

High-molecular-weight polymers can be useful as solid materials and in solution, and lower molecular weight polymers can make liquids that are unusual in character. Synthetic adhesives illustrate liquid-phase materials that cross-link or polymerize when they set. Water-based paints are another example, liquids with suspended solid polymer particles that form uniform solid films during drying. So-called liquid crystals illustrate another exciting example of complex fluid materials; these are liquid-phase materials made up of anisotropic, usually fairly rigid, molecules of high aspect ratio that have strong electric dipole moments. Such molecules are prone to adopt preferred orientations, especially under the influence of surfaces, electric fields, and flow processes. Control over preferred orientations gives high anisotropic strength of materials and switchable optical properties, making them useful in displays such as those on digital watches and laptop computers.

Multicomponent systems having molecules of macromolecular size and heterogeneous composition can be exquisitely sensitive to the delicate balance of intermolecular forces. The fine interplay among a suite of noncovalent interactions (e.g., steric, electrostatic, electrodynamic, and solvation forces) dictates microstructure and dynamics. Molecular organization and interaction cause collective and cooperative behavior to dictate macroscopic properties. Often the balance of forces is such that self-assembly occurs to generate aggregates, arrays, or other supramolecular structures. Large molecular size enables amplification of a small segmental effect into a large intermolecular effect. Self-assembly can amplify the small forces between small objects to produce large-scale structures useful for macroscopic creations for patterning, sieving, sorting, detecting, or growing materials, biological molecules, or chemicals. Learning to understand and harness intermolecular interactions in multicomponent polymer and composite systems offers huge challenges, as well as opportunities to mimic nature, which has learned to do this in many instances.

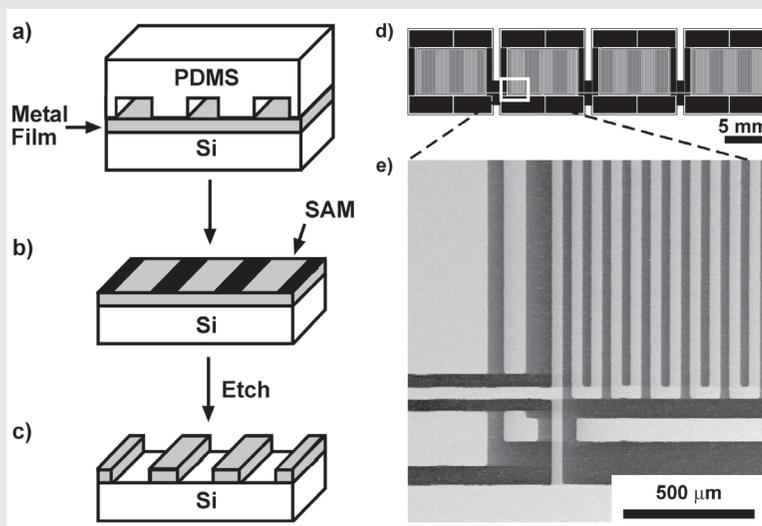
Self-assembled monolayers (SAMs) are ordered, two-dimensional crystals or quasi-crystals formed by adsorption and ordering of organic molecules or metal complexes on planar substrates. Development of these monolayers is based on early studies in which chemists learned to attach chemicals to surfaces—for purposes ranging from adhesion to chromatography to electrochemistry—but often without strong ordering in the monolayers. The ordered structures have made it possible to develop a rational surface science of organic materials. They provide the best current example of the power of self-assembly to make possible the design of the properties of materials. They have made routine the control of wetting, adhesion, and corrosion in certain systems, and—through soft lithography—they have provided a new approach to microfabrication that is uniquely chemical in its versatility. They have also greatly advanced the field of biomaterials by making it possible to control the interface between cells and synthetic materials at the molecular level.

## Soft Lithography

Building ever smaller devices has been a dominant trend in microelectronics technology for 50 years. The technology used for this type of fabrication is photolithography. This astonishingly sophisticated technology is a kind of photography: The pattern that is to be a part of the circuit is formed by shining ultraviolet light through a mask (a pattern of chromium on silica), through a reducing lens, onto a thin film of photosensitive polymer (a photoresist) covering the surface of a silicon wafer. After exposure, the exposed polymer differs in its solubility from unexposed material, and a suitable solvent allows the selective dissolution of either exposed or unexposed regions. The exposed regions are then treated (by deposition of metal, etching, or implantation of ions) to make a part of the final device.

Photolithography is the basis of one of the technologies that has genuinely changed the world—it has made possible the computing and information revolution. But it is not suited for making every possible type of small structure. As the advantages of “small” have become obvious in microelectronics, researchers have searched for ways to make small channels (for analysis of fluids or for synthesis), small machines (so-called microelectromechanical systems, or MEMS, for accelerometers and display projectors), and small optical systems (for optical communications). Such targets for fabrication all have different requirements in materials and costs, and photolithography is not a “one size fits all” technology.

An alternative to photolithography has been developed that is—for many applications in chemistry and biology—more versatile and much less expensive. This technology depends on a “back to the future” strategy that produces micron- and nanometer-scale patterns by stamping, printing, and molding. The element in these methods is a stamp or mold that is fabricated in a transparent, chemically inert elastomer, poly(dimethyl siloxane) (PDMS). Because the stamp can deform, it is called soft; the organic materials that are printed and molded are also called soft matter by physicists—hence the name soft lithography. Patterns of small features are embossed in the surface of the element; when it is “inked” with a suitable ink, it can print lines that are  $<100$  nm in width (that is, the size of a line of 200 gold atoms). As illustrated here, when the recessed regions are filled with a polymer, and the pattern is transferred to a surface, the resolution is  $<10$  nm. If the stamp is sealed to another surface, the patterns become microchannels for analysis of nucleic acids, proteins, or cells.



Soft Lithography. Figures a-c illustrate a soft-lithographic technique called microcontact printing. A PDMS stamp with features in bas-relief is coated with an ethanolic solution of octadecanethiol, and placed in contact with the surface of a thin metallic film (30-50 nm) of gold, silver, or palladium. A self-assembled monolayer (SAM) of octadecanethiolate forms on the surface of the metal in the regions where it contacts the PDMS stamp. The stamp is removed and the regions of the metallic film without a SAM are dissolved by wet-chemical etching. Figure d is a schematic diagram of a long, serpentine, palladium wire (2 m) with contact pads that are connected to the wire at every 0.25 m along the length of the wire; it is a part of a sensor for hydrogen. Figure e is a SEM image of a section of the pattern. Drawings a-c courtesy of George M. Whitesides; d-e reprinted with permission from D. B. Wolfe et al., *Applied Physics Letters* 80, 12, 2222 (2002).

Soft lithography is very simple, and it does not require expensive instrumentation or access to clean rooms. It does not give the lateral accuracy of photolithography, but it is much less expensive. The size of the features it can make is not limited by optical diffraction, but rather by van der Waals contacts and by deformations in the polymer used. It has become a tool that is widely used in chemistry to make micro- and nanostructures. It also has helped to open doors to chemists wishing to play an active role in many areas of cell biology, bioanalytical chemistry, microfluidics, optics, and new forms of electronics such as “all-organic” electronics: that is, electronics that does not rely on silicon, but instead uses organic or organometallic compounds as conductors, semi-conductors, and insulators.

Micelles, liposomes, shell-linked particles, and vesicles are all results of the spontaneous self-assembly of amphiphilic molecules to form enclosed or aggregate structures that contain solvophobic regions surrounded by solvent-loving moieties. In all of these structures, opportunities abound to exploit them for chemical separations, controlled release, directed transport, and synthesis. Fundamental studies of these organized systems have increased in the recent decade. The pursuit is often biologically inspired, but in creating mimics we still fall short of the natural systems. Combining this activity with concerted synthetic chemistry and biochemistry provides great potential for the future.

### **Electronic, Optoelectronic, Photonic, Magnetic, and Superconducting Materials**

The properties of modern electronic, optoelectronic, photonic, and magnetic devices provide another story of great science that has affected most of humankind. Electronic devices require special materials: materials that emit light when struck by a beam of electrons for use in television screens and computer monitors, materials to make the semiconductors that are the heart of electronic and microelectronic circuits, and materials that are used in magnetic memory storage devices for computers.

Classical electronic circuits and communication lines are made of metal to conduct electricity. Now we have the prospect of massively communicating by optical signals. The great progress in the use of optical fibers to permit light to travel in and between devices results from major achievements in materials processing. Special surface coatings on the fibers reduce signal degradation; optical switches allow connections with devices communicating through optical fibers. The optical fiber revolution provides very high speed plus the ability to pack much more information into a given transmission.

There is considerable interest in developing new types of magnetic materials, with a particular hope that ferroelectric solids and polymers can be constructed—materials having spontaneous electric polarization that can be reversed by an electric field. Such materials could lead to new low-cost memory devices for computers. The fine control of dispersed magnetic nanostructures will take the storage and tunability of magnetic media to new levels, and novel tunneling microscopy approaches allow measurement of microscopic hysteresis effects in iron nanowires.

One of the most exciting properties of some materials is superconductivity. Some complex metal oxides have the ability to conduct electricity free of any resistance, and thus free of power loss. Many materials are superconducting at very low temperatures (close to absolute zero), but recent work has moved the so-called transition temperature (where superconducting properties appear) to higher and higher values. There are still no superconductors that can operate at room temperature, but this goal is actively pursued. As more current is passed through

a superconductor the transition temperature moves lower; consequently, high electrical current tends to make the materials lose their superconducting ability. The development of a full, predictive theory of high-temperature superconductivity would be a major asset to the realization of practical materials in this area. The materials studied to date are also difficult to process—they are easily corroded or brittle—thus motivating further study of novel processing or assembly techniques. If practical superconductors can be made that will conduct appreciable currents at reasonable temperatures—perhaps even from organic materials—it may become possible to transfer electric power over long distances with high efficiency, and to exploit magnetic levitation for transportation systems.

### Quantum Computation

The first demonstration of continuous electrical tunability of spin coherence (the state and degree of alignment of electronic spins) in semiconductor nanostructures has recently been made. This opens possibilities for the field of quantum computation by permitting properties other than electronic charge—and particularly the quantum property of spin—to be manipulated for computing purposes. Spin, often described by analogy with rotation of the earth, is a quantum property of electrons (and some atomic nuclei) that must have one of two possible values analogous to clockwise or counter-clockwise rotation of a rotating body.

While magnetic fields are conventionally used to manipulate spins in familiar magnetic devices like hard-disk drives, this demonstration of electrical control of aligned spins represents a significant step toward making new spin-based technologies. One future technology is quantum computing, where many schemes make use of electron spin states as bits of information analogous to the 0 and 1 of binary computing. Unlike ordinary bits, *quantum bits* can be any combination of both 0 and 1 simultaneously, corresponding to a continuous range of possible directions.

By classical mechanics, magnetic fields can modify the behavior of spins by inducing precession, which is an additional rotation of the spin axis with respect to the magnetic field. While the speed of electron spin precession in a magnetic field is generally fixed by the particular materials used, recent research has shown that both the speed and direction of precession can be continuously adjusted by applying electric fields in specially engineered quantum structures.<sup>3</sup> It is more fitting to refer to

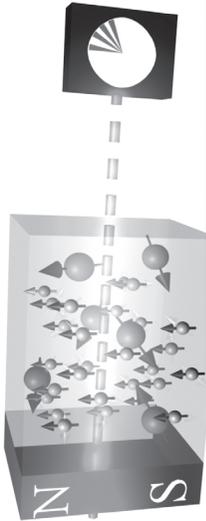
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<sup>3</sup>G. Salis, Y. Kato, K. Ensslin, D. C. Driscoll, A. C. Gossard, D. D. Awschalom, *Nature*, 414, 619, 2001

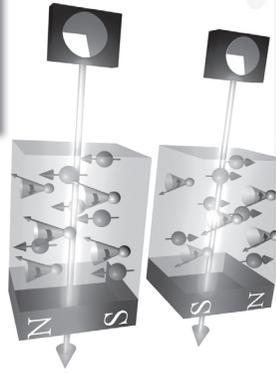
# New Magneto-Optical Spin Control for Spintronics



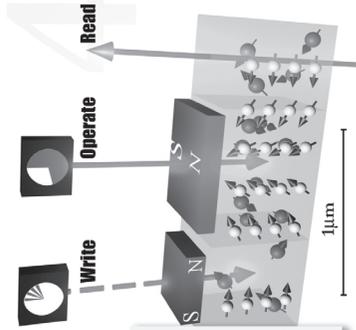
Electrons and nuclei have tiny magnetic moments due to their "spin", but enormous magnetic fields are needed to align them. The fields necessary are hundreds to thousands of times stronger than the average refrigerator magnet!



Researchers found that within picoseconds of absorbing an ultrashort laser pulse, electron spins in a semiconductor (GaAs) spontaneously polarize along the magnetization of a thin ferromagnetic layer, such as Iron (Fe), deposited on top of the GaAs.



Another surprise was that nuclear spins also become polarized by the magnetic layer after several minutes. This polarization acts like a magnetic field causing electron spin to "precess" at a frequency and in a direction controlled by the magnetic layer.



A future optical device exploiting these two discoveries could write, read and operate on electron spins, while using patterned magnetic regions as memory elements. The region of large nuclear polarization rotates electron spins as they pass by— one necessary operation for "quantum computing."

these devices as gates rather than switches because they perform continuous tuning of electron spin. Instead of the “off” and “on” options for a switch, a gate operates across a continuum in the same way that lights can be dimmed by a rheostat.

Such spin gates are an example of the rapidly developing field of spintronics, which studies electronic devices that are based on electron spin. *Spintronics* uses magnetic fields to manipulate the distribution of spin coherence, whereas *electronics* uses electric fields to manipulate charge distribution. This raises the question, What might spintronics do that electronics cannot? In addition to the longer-term goal of quantum computing, spintronics offers the near-term possibility of revolutionizing the way we think about piecing together different technologies.

The creation of nanoscale sandwiches of compound semiconductor heterostructures, with gradients of chemical composition that are precisely sculpted, could produce quantum wells with appropriate properties. One can eventually think of a combined device that incorporates logic, storage, and communication for computing—based on a combination of electronic, spintronic, photonic, and optical technologies. Precise production and integrated use of many different materials will be a hallmark of future advanced device technology.

The opportunities to develop new structures for computing, quantum computation, and spintronics—together with other areas in molecular electronics—raise important issues about the role of computation in the chemical sciences (Chapter 6). In order for chemical scientists to play a major role in converting clever new ideas for computational devices into full-fledged computers, they will have to become increasingly competent in the architectures, algorithms, and protocols that are necessary for reliable computation.

### **Ceramics, Carbon Structures, and Crystal Engineering**

Inorganic substances are the components of ceramics, such as those in dinner plates. Ceramics have important industrial uses as well; a typical example is the ceramic insulating materials that are used to suspend power lines. Ceramics are typically poor conductors of heat and electricity, and they perform well at high temperatures. Consequently, they find applications that take advantage of these properties. Some use of ceramics in automobile engines is being developed to achieve improved fuel efficiency at higher-temperature operation. The fragility of current ceramics and the difficulty in machining them (relative to machining

metals) are still problems for such uses. One approach to ceramics with better properties is to overcome their fragility by incorporating them into composites. As chemistry moves from pure materials to organized systems of different materials, composites are leading the way. A challenge for the future is to invent improved structural materials, probably composites based on resins or on ceramics, that are stable at high temperatures and easily machined.

Carbon atoms in pure form can be obtained as materials having two classic types of molecular structure: diamond and graphite. In diamond each carbon atom is linked by equivalent single bonds to four neighboring carbons. The result is a clear very hard material that is used for cutting, in saws with tiny diamonds imbedded in the blades, as tough coatings for metals, and in other industrial uses as well as in jewelry. By contrast, each carbon atom in graphite is linked to only three neighboring carbons, in a sheet, and some of the electrons are in delocalized pi orbitals that permit them to move easily along the sheets. The extensive aromaticity of carbon sheets leads to electronic transitions with energies in the visible light region, so that graphite absorbs throughout the visible region and is a black material. In addition, the mobility of the pi electrons in graphite makes it an electrical conductor, in stark contrast to the insulating properties of diamond.

A new type of structure has recently been discovered in which the sheets of graphite-like carbons are curved. The first example, called fullerene (after the geodesic domes of Buckminster Fuller), has 60 carbons in a sphere. It resembles a soccer ball with its five- and six-sided polygons (in contrast to graphite, which resembles a floor tile pattern, with hexagons only). A Nobel prize was awarded in 1996 to Robert F. Curl, Jr., Harold W. Kroto, and Richard E. Smalley for their discovery of fullerenes. Instead of curling into a sphere, the sheets of carbon with hexagons can also curve into tubes with diameters on the order of 1 nm (often called nanotubes), tiny whiskers that are sometimes quite long. Because of the electrical conductivity of pi electrons, these tubes are also electrically conducting, somewhat like graphite. While they are already used in research instruments to probe microscopic structures, one of the challenges is to use these new structures in miniature devices, or as building blocks for organized chemical structures.

The importance of crystal form often is underappreciated. In many applications—from drugs (in which bioavailability may be determined by crystal form) to explosives (where crystals may differ in stability) and optical devices (where the nonlinear optical properties required for the device are based on a particular crystalline architecture)—the correct crystalline form is essential to obtaining the desired chemical and physical properties of a material. Crystallization has long been an art rather than a science; sometimes the same substances will exhibit polymorphism and adopt different crystalline forms depending on the crystallization conditions. Crystal engineering—the prediction and control of molecular crystal structures based on the constituent molecular structures—is on the verge of becoming a science. The current generation of computers is finally powerful

enough to rationalize the crystal structures of simple, relatively rigid, organic molecules. As computer capability increases, and as the sophistication of the programs used increases, it seems very probable that it will soon be possible to predict the structures of crystals. Learning to template or guide desired organization of molecules will have great utility.

### Layered Materials and Surface Modification

The scale of components in complex condensed matter often results in structures having a high surface-area-to-volume ratio. In these systems, interfacial effects can be very important. The interfaces between vapor and condensed phases and between two condensed phases have been well studied over the past four decades. These studies have contributed to technologies from electronic materials and devices, to corrosion passivation, to heterogeneous catalysis. In recent years, the focus has broadened to include the interfaces between vapors, liquids, or solids and self-assembled structures of organic, biological, and polymeric nature.

In a simple material, its surface properties are dictated by the properties of the bulk, which are not necessarily desirable. For example, we may need a bulk material for its strength but want to make a medical device—such as an artificial heart—where the surface must not cause a reaction leading to rejection or blood clotting. This leads to the challenge of learning how to add biocompatible surface layers to materials. This challenge is not yet fully met, but interesting approaches to creating biomimetic functionality on surfaces are rapidly emerging. This field is an example of the transition of chemistry from pure materials to organized systems and materials, in this case the organization being the modification of the surface with a different material for a biofunctional purpose.

The ability to modify surfaces by attaching chemicals to them has for years encouraged scientists to attempt to design surface adhesive and wetting properties. The advent of self-assembled monolayers, including mixtures of molecules in a monolayer, has led to more detailed control and understanding of surface adhesion and wetting. This capability has been extended with the use of novel monolayers to alter liquid-crystalline anchoring processes, surface friction, and biocompatibility. Important applications of this approach have arisen in microfluidics and liquid crystalline displays. Work pioneered by Nuzzo and Allara at Bell Laboratories in the early 1980s with thiol self-assembled monolayers on gold has led to a great deal of research, much of which has been revolutionary.

Thus the study of surfaces has emerged as an important focus in the chemical sciences, and the relationship between surfaces of small systems and their performance has emerged as a major technological issue. Flow in microfluidic systems—for example, in micromechanical systems with potential problems of stiction (sticking and adhesion) and for chemistry on gene chips—depends on the properties of system surfaces. Complex heterogeneous phases with high surface areas—suspensions of colloids and liquid crystals—have developed substantial

technological importance. In certain size ranges, we have seen new and scientifically engaging phenomena, such as electron tunneling through nanometer-thick insulators and diffraction of light in photonic band-gap crystals. New tools and systems—from scanning tunneling microscope and atomic force microscope (STM and AFM) to self-assembled monolayers and carbon nanotubes—have fundamentally changed our ability to characterize and prepare these complex systems. Finally, microelectronics—complex systems of small functional components fabricated in silicon and silicon dioxide, and other materials—have become so important that we must develop the science and technology relevant to future systems of small components, whether based on microelectronics or other technologies. The microelectronics industry is entirely based on chemical processing, using such techniques as chemical vapor deposition (CVD), plasma processing, etching, and electroless deposition.

### Nanomaterials

As the analytical, synthetic, and physical characterization techniques of the chemical sciences have advanced, the scale of material control moves to smaller sizes. Nanoscience is the examination of objects—particles, liquid droplets, crystals, fibers—with sizes that are larger than molecules but smaller than structures commonly prepared by photolithographic microfabrication. The definition of nanomaterials is neither sharp nor easy, nor need it be. Single molecules can be considered components of nanosystems (and are considered as such in fields such as molecular electronics and molecular motors). So can objects that have dimensions of  $>100$  nm, even though such objects can be fabricated—albeit with substantial technical difficulty—by photolithography. We will define (somewhat arbitrarily) nanoscience as the study of the preparation, characterization, and use of substances having dimensions in the range of 1 to 100 nm. Many types of chemical systems, such as self-assembled monolayers (with only one dimension small) or carbon nanotubes (*buckytubes*) (with two dimensions small), are considered nanosystems.

Whether there is currently a *nanotechnology* is a question of definition. If one asks whether there are (or are soon likely to be) commercial electronic fluidic, photonic, or mechanical devices with critical lateral dimensions less than 20 nm, the answer is “no,” although there may be in 10 to 20 years. There is, however, a range of important technologies—especially involving colloids, emulsions, polymers, ceramic and semiconductor particles, and metallic alloys—that currently exist. But there is no question that the field of *nanoscience* already exists.

The current, intense interest in “nano” is based on the (correct) perception that the study of nanoscience has exploded. As new tools have become available for the preparation and characterization of systems with these dimensions, the opportunities in the chemical sciences have grown enormously. The attention

also results from the as yet untested proposition that nanoscience will eventually revolutionize existing areas of important technology, especially microelectronics.

There is great interest in the electrical and optical properties of materials confined within small particles known as nanoparticles. These are materials made up of clusters (of atoms or molecules) that are small enough to have material properties very different from the bulk. Most of the atoms or molecules are near the surface and have different environments from those in the interior—indeed, the properties vary with the nanoparticle's actual size. These are key players in what is hoped to be the nanoscience revolution. There is still very active work to learn how to make nanoscale particles of defined size and composition, to measure their properties, and to understand how their special properties depend on particle size. One vision of this revolution includes the possibility of making tiny machines that can imitate many of the processes we see in single-cell organisms, that possess much of the information content of biological systems, and that have the ability to form tiny computer components and enable the design of much faster computers. However, like truisms of the past, nanoparticles are such an unknown area of chemical materials that predictions of their possible uses will evolve and expand rapidly in the future.

Several techniques are now available for the fabrication of nanostructures. These techniques arise from four approaches, and their simultaneous applicability to a common set of targets is one of the reasons for the excitement in the field. The first set includes the classical techniques developed from microfabrication:

- electron beam writing, which is the most important, although x-ray and deep UV photolithographies may also contribute;
- use of scanning probe devices to move individual atoms or to write patterns;
- preparation of colloids, vesicles, emulsions, buckytubes, and self-assembled monolayers using chemical self-assembly methods (some with histories that date back to the beginning of chemistry);
- soft lithography and nanoimprint lithography, which use printing, molding, and embossing technologies developed on the macroscopic scale to replicate structures at the nanoscale.

The characterization of simple nanostructures is now possible with remarkable detail, but is highly dependent on access to the tools of measurement science and to scanning probe microscopies.

These methods have made available a set of nanostructured systems that have begun to reveal the characteristics of nanoscale matter. The long list of discoveries in the last decade includes:

- “quantum box” behavior in colloids of semiconductors precipitated from solution;

- quantized capacitive charging of metal nanoparticles coated with low dielectric monolayers;
- a range of electrical properties in carbon nanotubes grown from vapor-phase precursors using metallic catalysts (with the highest observed conductivities comparable to those observed in graphite);
- high mechanical strength of buckytubes (combined with the above-mentioned electrical properties) that makes them possible candidates for “nanowires”;
- remarkably regular nanostructures in phase-separated block copolymers;
- functional transistors prepared in organic semiconductors with 100-nanometer gate widths;
- membranes containing nanopores with controlled interior functionality;
- versatile methods of preparing nanostructures that are based on simple ideas taken from printing, writing, molding, and embossing, and that have made it possible to prepare certain nanostructures without use of expensive apparatus.

Two important conclusions have emerged in this field. First, the methods employed for microelectronics—photolithography using UV wavelengths—are unlikely to provide inexpensive access to nanostructures. Second, the techniques of chemistry and chemical engineering—although very early in their development—will be able to provide nanostructures with a wide range of compositions and properties, and at costs that are very low compared to those prepared by e-beam or other “conventional” techniques for fabrication at small dimensions. In particular, chemical affinities should make it possible for tiny structures and devices to self-assemble spontaneously, an appealing idea for large-scale manufacturing.

## CHALLENGES AND OPPORTUNITIES FOR THE FUTURE

Many of the challenges of the formation and processing of new materials will be met with advances in the chemical sciences. There are some revolutionary things happening in materials: organic electronics and spintronics, attempting to replace classical silicon electronics, the exploration of single-molecule electronics to achieve the ultimate in size reduction, sophisticated biocompatible materials for tissue engineering, implants, man-machine hybrids, ferromagnetic organic materials, materials with negative index of refraction, nanoelectronics, and functional colloids.

Self-assembly and nanotechnology are advancing rapidly, but the challenge still remains to develop a means of fabrication and manufacturing. The rapid developments in synthetic chemistry produce myriad new polymeric and composite materials. These advances are enhanced by progress in optical, micro-mechanical, and spectroscopic probes. The miniaturization and diversification of synthesis through biological or combinatorial approaches provide unprecedented

opportunities. The approach to the future should be a holistic one, with synthetic advances moving in concert with assembly and microstructural control. Summarized below are a few of the leaps that can be viewed as important aspirations for the chemical science community.

### **Templating**

The development of templated syntheses—of metallic, ceramic or semiconductor particles, wires using novel synthetic and self-assembling structures such as dendrimers, micelles, and nanotubes—is in its infancy. This is a prime example where synthetic advances in the creation of new lipids, surfactants, and amphiphilic polymers work together with probes of structure and function of infinitesimal wires or particles. New techniques such as scanning microscopy must be developed to follow the electronic and magnetic processes occurring in the small systems. Spectroscopists, microscopists, engineers, and chemists must work together at the frontiers involving techniques developed by those from disparate fields of electronics and biology.

### **Higher Order Structures**

The ability to program synthetic polymers with the correct information to self-assemble, recognize analytes, or provide biological function seems fairly futuristic. However, the close interplay between chemical composition and physical interactions makes this a possibility; new synthetic approaches involving controlled living polymerizations and biological synthetic pathways allow control of molecular composition. Additional research on the balance of physical forces driving self-assembly, recognition, field responsive behavior, and biological compatibility should be closely tied to the synthetic efforts.

New approaches in synthetic chemistry and biochemistry pave the way for tremendous advances in self-assembly. Highly controlled living polymerizations will allow the creation of ever more complex macromolecules having prescribed architectures (branching, stereoregularity) and chemical specificity. The future will hold the opportunity for chemists to make molecules of size and complexity approaching protein structures—and to fold and assemble them. Then, mimicking nature becomes a question of choosing important problems and technologies needing improvement or intervention. By creating the appropriate molecules, patterning them on the appropriate surfaces, and providing them with the appropriate functions, we can think of mimicking the most chemical of senses: taste and smell. These analytic advances, when taken in parallel with the computational and electronics revolution, suggest the possible creation of the robots and gadgets that were previously envisioned only in science fiction.

### **Semiconductor Processing**

We need novel materials to maintain the computer revolution, since we may be reaching the limits of “top down” miniaturization. Instead of etching pieces of silicon to produce electronic circuits that are smaller and smaller, there is the hope that “bottom up” design will work. In other words, self-assembly of molecules or nanoparticles offers the potential for construction of miniature electronic circuits that will be faster and will permit more computer power in a given space. Promising physical approaches involve soft-lithography or crystal or nanoparticle growth, but other processes doubtless will emerge as the field of nanoparticle science evolves.

Chemical scientists will seek new methods of generating nanostructures with a range of materials and processes that rely on ideas common in chemistry—self-assembly, diffusion, phase-separation, catalysis, wetting—to make these structures accessible and inexpensive.

In terms of technology, it is too early to predict what will emerge from nanoscience, although it is clear—for a field as fundamental as this one—that technologies will surely emerge. Candidates for early success include systems of photoluminescent colloids in which the same materials base provides any desired color simply by tailoring the size (for displays); compact disks with <50-nanometer pits (for very dense memory devices that will require near field recording technology); and optical elements for manipulating extreme UV and x-ray light. In the longer term, there will be, at minimum, demonstrations of information processors having key components with nanometer dimensions (perhaps made of organic or organometallic materials) and probes for exploring the interior of the cell.

As self-assembly and nanotechnology move from curiosities and demonstrations to more serious means of fabrication and manufacturing, the need for characterization tools, especially those that can meet the time scales for real-time processing, will grow enormously.

### **Molecular Electronic Materials**

Improving the molecular control of addressable, switchable, or conducting molecules that have extremely high purity, selectivity, or specificity is a goal within reach in the coming decades. This will require the combination of synthetic and processing strategies, such as recognition and controlled binding, to tailor oligomeric materials with finely tuned properties. In this field, the chemical sciences will have to interact creatively with computer science and engineering in order to turn promising molecular switching ideas into practical computer architectures.

## Composite and Hybrid Materials

As the ability to control materials moves to molecular dimensions, the expectations for composite materials will grow. Rather than relying on incorporation of macroscopic particles or fibers as discussed above, one can hope to create important marriages between disparate materials that will allow the development of new material properties. Combining this synthetic expertise with physical patterning, self-assembly, deposition, or quenching techniques will lead to the creation of new materials with optimal properties. Organized nanocomposite materials can be important for photonic band gap materials as well as membranes and catalysts with high selectivity.

## Surface Modification and Interfaces with Biology and Electronics

The connection between biological function and a useful electrical signal is the capstone of sensor technology that will change medical, environmental, and personal-protection strategies in the coming decades. The link between biology and electronics is through the chemical sciences. The ability to mimic nature and reliably anchor biologically active moieties to a surface is in its infancy. Here another level of complexity and functional integration are possible. Coupling the physical chemical means to manipulate interfaces with synthetic strategies inspired by nature provides powerful opportunities for gains in environmental and medical devices. As an example, the recent understanding of virus phage packaging, combined with the ability to inject DNA into a host or a host mimic, opens the way for molecular scientists to develop new therapies and delivery strategies. Another challenge is the construction of materials with the kind of actuating response found in physiological systems such as muscle—soft materials in which a large-amplitude mechanical response could be produced in response to a small-amplitude stimulus.

Capitalizing on self-assembly and nanoscience will enhance the ability to screen drugs for individual sensitivities. Advances in drug discovery, combinatorial synthesis, and screening with sensors that have the ability to detect multitudes of specific genetic matches—marrying microelectronics and self-assembly—are expected to be near-term breakthroughs. Then the creation of advanced forms of “in the field” or “in the office” tests for chemical risks, pharmaceutical compatibility, or environmental hazards will be possible.

The processing of materials through self-assembly will also have to meet several kinds of challenges that arise from scaling up in physical size and speed, and in complex shapes. Little has been done with complex shapes and nonplanar surfaces. Can processes that work on glass slides or mica or 4-inch silicon wafers be scaled up to very large surface areas, such as continuously moving webs of paper, film, or tape, or surfaces of tubular biomaterials? Building large volumes

of nanostructured, self-assembled materials in three dimensions may be even more challenging than scaling up to large surfaces.

Processing speed presents different challenges. Since self-assembly is a process that moves down a free energy gradient, there is a predetermined end point; but it is not known how to anticipate its speed. Study of the kinetics and dynamics of self-assembly processes will be necessary to bring this field to a level comparable to traditional methods of synthetic chemistry and chemical engineering. Few studies of kinetics of assembly processes have been pursued, in part because following the assembly process presents analytical difficulties. Practical processing rates will certainly have to be much faster than those of typical current research laboratory practice. The free energy landscapes along the paths toward self-assembled products are not fully explored. Local minima and metastable states lurk but are uncharted, and it is often not appreciated when they are occupied or when they are trapping the process far from the desired equilibrium state. The challenges of kinetics and of metastable states raise the question of catalysis and whether routes to assist, accelerate, and guide self-assembly processes can be developed.

Self-assembly processes in nature are sometimes catalyzed by enzymes. Zeolites are, in many ways, the inorganic counterparts of enzymes, with their ability to selectively bind other substances and perform catalysis. Can templates or catalysts be effective in increasing rates and reducing defects in a wide range of nanostructured materials?

One of the most general forms of the surface modification of materials is *painting*. We have become used to the idea that paints, while serving their important function of preventing corrosion and water damage, need to be renewed on a regular basis, with a significant cost in labor and materials. One less glamorous challenge that could make a significant contribution to modern life is the invention of long-lasting paint, perhaps 100-year paint. In addition, it would also be desirable that this long-lasting paint be easily cleaned, perhaps simply by natural rain, and that it have a mechanism to repair damage to itself. We are used to the idea that our body can repair wounds; it is an important challenge to devise methods by which synthetic materials would also have this wound-healing ability. As one approach, the wound might expose pools of monomer that could spontaneously fill the void and solidify.

### **Green Materials and Eco-Technology**

Other challenges facing materials scientists have to do with the environment. We have traditionally made materials that are as stable as possible, so they will last a long time and not need to be replaced. This longevity has the undesirable consequences of creating waste that requires significant energy to process, or else it clutters the landscape when discarded. As one approach, chemical scientists and engineers need to focus on recycling and materials that can be easily re-

cycled. Another approach is to produce materials that undergo rapid degradation into invisible and harmless substances. Some progress has been made by incorporating ketone groups into polyethylene so that sunlight will break chemical bonds and cause the polymer to disintegrate into tiny particles. However, these materials are not yet economically attractive, and more efforts of this kind are needed.

This is part of the general need, discussed in Chapter 9, to make materials such as insecticides or refrigerants that will degrade in the environment rather than cause problems with bird life or with the ozone layer in the stratosphere. In addition, as the world demand for synthetic materials grows, new renewable resources for chemical feed stocks must be sought, and we must reconsider our current infatuation with burning the petroleum reserves that are important feedstocks (as discussed also in Chapter 10). Zero-effluent processing plants also need to be developed. There are innumerable opportunities for advanced chemical processing of materials to create micro- and nanodevices for environmental and ecological monitoring.

Another challenge is to develop methods to replace the volatile organic solvents that are used in many industrial procedures. One choice is water as a solvent; it is easily repurified, and has a harmless vapor. Another choice is supercritical carbon dioxide, a good solvent for many organic substances. It is not as innocuous as is water, but carbon dioxide can be easily recovered and reused. It is currently used to remove caffeine from coffee, and is being developed as a dry-cleaning solvent to replace organic solvents (Chapter 9).

### **Analysis and Simulation**

Advances in computational capability have raised our ability to model and simulate materials structure and properties to the level at which computer “experiments” can sometimes offer significant guidance to experimentation, or at least provide significant insights into experimental design and interpretation. For self-assembled macromolecular structures, these simulations can be approached from the atomic-molecular scale through the use of molecular dynamics or finite element analysis. Chapter 6 discusses opportunities in computational chemical science and computational materials science.

Molecular dynamics simulations are capable of addressing the self-assembly process at a rudimentary, but often impressive, level. These calculations can be used to study the secondary structure (and some tertiary structure) of large complex molecules. Present computers and codes can handle massive calculations but cannot eliminate concerns that boundary conditions may affect the result. Eventually, continued improvements in computer hardware will provide this added capacity in serial computers; development of parallel computer codes is likely to accomplish the goal more quickly. In addition, the development of realistic, time-efficient potentials will accelerate the useful application of dynamic simulation to the self-assembly process. In addition, principles are needed to guide the selec-

tion of initial configurations; the proper initial conditions accelerate convergence and minimize problems associated with metastable configurations.

Molecular calculations provide approaches to supramolecular structure and to the dynamics of self-assembly by extending atomic-molecular physics. Alternatively, the tools of finite element analysis can be used to approach the simulation of self-assembled film properties. The voxel<sup>4</sup> size in finite element analysis needs be small compared to significant variation in structure-property relationships; for self-assembled structures, this implies use of voxels of nanometer dimensions. However, the continuum constitutive relationships utilized for macroscopic-system calculations will be difficult to extend at this scale because nanostructure properties are expected to differ from microstructural properties. In addition, in structures with a high density of boundaries (such as thin multilayer films), poorly understood boundary conditions may contribute to inaccuracies.

Image analysis is an important aspect of many areas of science and engineering, and imaging will play an important role in characterizing self-assembled structures as well as in on-line process control. Development of effective noise identification and suppression, contrast enhancements, visualization, pattern recognition, and correlation algorithms should be co-opted where possible and adapted to the analysis of self-assembled structures.

Models of the self-assembly process also will be important. Because self-assembled structures can be diverse, those models are likely to be highly complex. Sensitivity analysis can be an important approach to the identification and control of critical parameters.

### Adaptive and Responsive Materials

An area of great promise for the future is that of materials for which properties change in response to external influences. The most prominent is giant magnetoresistive (GMR) materials—materials for which the electrical conductivity can change by a few percent under the application of an external magnetic field. GMR materials moved from a laboratory curiosity to the dominant technology in computer memories within a decade—a startling example of how a new material can completely change a major industry. The invention of new materials has been an area in which the United States has played a central role; the current emphasis on focused, shorter-term projects has, however, made it very difficult to support a lively activity in new materials, which by definition are far from a final product.

Among the adaptive materials currently on the forefront are liquid crystals, electro- and magneto-rheological (ER/MR) fluids, thermo- and physioreponsive gels, and shape memory alloys. In all but the last case, these systems involve

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<sup>4</sup>A *voxel* is a volume-pixel. While a pixel is a two-dimensional point that has the attributes of height and width, a voxel is a three-dimensional point with the attributes of height, width, and depth.

fluid-solid interfaces, complex or dispersed suspensions, and external fields. Thus, all of the directions outlined above for self-assembly and interfaces come into play when pursuing these “smart fluids.” Improvements in synthesis and spatial resolution of the external fields through soft-lithography (self-assembled monolayers, etc.) will provide new capabilities of control and tuning of these complex fluids.

### **Tools, Resources, and Infrastructures**

The area of complex condensed matter depends crucially on the availability of appropriate tools for both fabrication and characterization. These tools are of “intermediate” size: they are neither a test tube nor a synchrotron. Typical tools—scanning probe microscopes, x-ray photoelectron spectrometers, electron microscopes, clean rooms—cost from \$0.1 million to \$5 million. They are shared-use facilities, but they must be local to the user group—travel to distance facilities for routine measurements is not practical.

Simulations in this area also require access to high-level computational capabilities. By definition, simulations involve both large numbers of atoms and dynamic behavior; both consume large numbers of CPU cycles. Because the field is so demanding on computer time, analytical theory is very important, even if it yields only approximate solutions.

Many of the tools required for the nanoscience revolution in materials involve sophisticated experiments requiring leadership, training, and infrastructure. User facilities such as high-resolution electron microscopes, synchrotrons and NMR facilities need to be easily accessible and provide adequate support for efficient experimentation.

The nanometer- to micrometer-scale dimensions of supramolecular assemblies present many challenges to rigorous compositional and structural characterization. Development of adequate structure-property relationships for these complex hierarchical systems will require improved measurement methods and techniques. The following areas constitute critical thrusts in instrument development.

- Many techniques ideally suited for nanostructure characterization unfortunately depend also on the substrate properties. For example, the reflectivity and conductivity of a substrate play an important role in the successful execution of the instrumental method. Hence, substrate-independent techniques are needed so that structure and/or behavior of the material can be investigated in a confined geometry, decoupled from the potentially invasive effect of the substrate-material interface.
- Feedback provided by on-line monitoring of self-assembling processes will play an increasingly important role in controlling the microscopic and macroscopic architecture of molecular assemblies. Successful adaptation of char-

acterization methods for noninvasive in situ monitoring will require miniaturization of many of the analytical devices commonly used for interrogating self-assembled structures. The revolution in microscopic identification and control provides new opportunities for chemists and chemical engineers. Promising routes to achieve this goal include the use of optical fibers in spectroscopic methods and the development of MEMS-based analytical instrumentation.

- Order and polydispersity are key parameters that characterize many self-assembled systems. However, accurate measurement of particle sizes in concentrated solution-phase systems, and determination of crystallinity for thin-film systems, remain problematic. While inverse methods such as scattering and diffraction provide measures of these properties, often the physical information derived from such data is ambiguous and model dependent. Hence development of improved theory and data analysis methods for extracting real-space information from inverse methods is a priority.

- Use of diverse techniques provides significant structural information in dispersed and thin-film systems. If significant advances in source intensities (e.g., higher neutron and x-ray fluxes, higher power diode lasers) and photon detector technology (e.g., high quantum efficiency, large bandwidth charge-coupled devices, CCDs) are achieved in the near term, these methods could be extended readily to studies of nanoscale features. Since the experimental and theoretical frameworks for these techniques are well established, extension to smaller length scales should be straightforward.

- The already critical need for molecular-scale compositional mapping will increase as more complex structures are assembled. Currently, electron microscopy, scanning probe microscopy (SPM) and fluorescence resonance energy transfer (FRET) are the only methods that routinely provide nanometer resolution.

In contrast to the mature instrumental techniques discussed above, a hitherto nonexistent class of techniques will require substantial development effort. The new instruments will be capable of measuring the thermal (e.g., glass transition temperatures for amorphous or semicrystalline polymers and melting temperatures for materials in the crystalline phase), chemical, and mechanical (e.g., viscoelastic) properties of nanoscale films in confined geometries, and their creation will require rethinking of conventional methods that are used for bulk measurements.

### WHY ALL THIS IS IMPORTANT

Materials science and engineering is inseparable from chemistry and chemical engineering. The importance of materials is illustrated by the effects they have on the quality of human life—underscored by the way our society uses new

materials and the technology they spawn to define epochs in history. The list of the 20 greatest engineering achievements of the 20th century, compiled in 2000 by the National Academy of Engineering,<sup>5</sup> contains many entries (for example, high-performance materials, automobiles, airplanes, electronics, computers, telephones, and fiber optics) that depend essentially on advances in materials science and engineering. From synthesis to processing to commodity manufacturing of materials, the tools of chemical science and engineering will be essential to defining the next century in these terms. New materials with predictable properties will provide worthy and formidable targets for design and synthesis, while processing and manufacturing these new materials will present significant challenging new objectives for chemical process-systems engineering.

The science of materials reflects the way that chemistry has changed—from a field concerned only with atoms and molecules and their properties in isolation, to a field increasingly concerned with organized interactive systems. This change opens opportunities and challenges in fundamental science that will let us ask not just: What are the chemical components of that stuff? We will be asking as well: How do those components interact to produce the properties of that stuff? The answers to such questions will greatly add to our understanding of the chemical universe.

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<sup>5</sup><http://www.greatachievements.org/>

# Atmospheric and Environmental Chemistry<sup>1</sup>

## **Some Challenges for Chemists and Chemical Engineers**

- Elucidate the entire complex interactive chemistry of our biosphere—the atmosphere, the earth, and its lakes, rivers, and oceans—and provide the scientific basis for policies that preserve our environment.
- Ensure that chemical manufacturing and chemical products are environmentally and biologically benign, never harmful.
- Learn how to make products that are stable over their necessary life but then undergo degradation so they do not persist in the environment or in living creatures.
- Invent agricultural chemicals that do not harm unintended targets in any way and are not overly persistent.
- Develop selective catalysts that enable the manufacture of useful products without producing unwanted waste products and without using excessive energy.
- Invent processes for the generation and distribution of energy that do not release greenhouse gases or toxic contaminants into the atmosphere.
- Help humans control their population growth by inventing birth control methods that are safe and effective, inexpensive, and widely available and accepted.

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<sup>1</sup>As part of the overall project on Challenges for the Chemical Sciences in the 21st Century, a workshop on The Environment will lead to a separate report. The reader is urged to consult that report for further information.

## GOALS

Chemists and chemical engineers want to understand the chemical composition and behavior of the earth, its rivers, lakes, and oceans, and its atmosphere. What are the complex interactions among these systems that occur naturally, how are they influenced by human activity, and what will be the chemical and physical consequences that affect our environment? To what extent can the knowledge and capabilities of chemists and chemical engineers be used to understand and prevent or correct problems, either by direct chemical intervention or by guiding changes in human behavior? As a society, we want to be assured that the products we use are safe for us and our environment—and to be sure that the methods of their production do not harm us, our children, or our environment. The safety of our environment is not a local issue. Concerns about global climate change make it clear that chemists and chemical engineers will want to help—and will need to help—in addressing these important scientific issues on a worldwide basis.

Systems in place—ranging from laws and policies of government regulatory bodies to voluntary programs of the industry—are intended to anticipate, detect, and prevent unacceptable risks to the public, both now and in the future. The ability of chemists and chemical engineers to meet these challenges, as contributors to and beneficiaries of the chemical enterprise, requires that they utilize the best science available today and aggressively advance that science in the future. This ability will also be enhanced by educational efforts—not only efforts by the scientific community to increase public understanding of science and technology, but also changes in the ways that engineers and scientists are educated. Greater understanding of the societal implications of their work by scientists and engineers will enhance our stewardship of this planet.

## PROGRESS TO DATE

Geochemists have made major progress in learning about the chemistry of the earth and its components, including rivers, lakes, and oceans. Much of this involves such fundamental theories as thermodynamics, but on a scale much larger than the molecular level that has been the past focus of the chemical sciences. In the last decade, the chemistry of the atmosphere has also been elucidated in much more detail. A field called earth systems engineering is emerging, and it will require further development, with the chemical sciences and engineering as a crucial component. This field will address matters such as global warming, carbon sequestration, and environmentally benign manufacturing. It will also address new analytical, computational, and assessment techniques through which global-scale interactions in complex systems can be better understood and optimized. Earth systems engineering is made even more intricate and involved by its international character. The factual, quantitative, and analytical input that can be supplied by chemical scientists will be of great value in this endeavor.

Chemists and chemical engineers have identified the processes that convert ordinary oxygen molecules ( $O_2$ ) into ozone ( $O_3$ ) in the high altitude ozone layer of the stratosphere, under the influence of ultraviolet light from the sun. Furthermore, chemists and chemical engineers have elucidated, through both experimentation and computational modeling, the processes by which extremely stable anthropogenic (human-generated) gases such as chlorofluorocarbon refrigerants cause degradation and depletion of the ozone layer. The ozone layer plays an important protective role for life on earth by blocking very-high-energy ultraviolet light; consequently, this fundamental atmospheric chemistry has important practical consequences. Similar understanding of the interaction of anthropogenic materials with water and with the minerals of the earth is also being developed by geochemists.

The chlorofluorocarbon effect on the ozone layer illustrates another chemical concern—the special problem that can arise when materials released into the environment are able to act as catalysts. If every chlorine atom generated in the upper atmosphere simply destroyed one ozone molecule, the effect would be minimal. But chemists have elucidated the catalytic cycle by which each chlorine atom destroys thousands of ozone molecules. It is particularly important for chemists to study and understand which substances can have such catalytic effects—and to learn how to prevent the release of such substances into the environment.

The interaction of gases such as carbon dioxide ( $CO_2$ ) with earth and water has also been investigated. Carbon dioxide is in most respects a harmless molecule—the product of human, animal, and plant respiration and the starting material for the growth of plants by photosynthesis. It is also produced by burning carbonaceous fuels for energy, and in converting limestone to lime for cement production. It is now becoming clear that too much carbon dioxide in the atmosphere can contribute to what is called the greenhouse effect. The temperature of the earth's surface is governed by what happens to the energy in incident sunlight—how much of it is reflected back into space versus how much is retained by conversion into thermal energy, and how much of that is reemitted back into space as infrared radiation. There is a delicate balance among these processes, and a change in that balance can affect the overall temperature of the earth. Greenhouse gases absorb some of this infrared radiation and prevent its transmission back into space. Other gases, particularly water vapor, also contribute to the greenhouse effect, but carbon dioxide is of particular importance because  $CO_2$  levels correlate with human activity. For this reason there has been extensive debate about the extent to which global climate change is anthropogenic.

Recent estimates indicate that the level of carbon dioxide in the atmosphere has increased by a third since the beginning of the industrial age, and that it contributes significantly to global warming. Other major contributors include methane, tropospheric ozone, and nitrous oxide. Methane is the principal component of natural gas, but it is also produced by other sources such as rice paddies and farm animals. Tropospheric ozone is generated naturally and by the sunlight-

induced reactions of combustion by-products, and nitrous oxide is formed in microbial reactions, in part from nitrogen-containing fertilizers, and as a by-product of some chemical processes. Carbon dioxide and methane—generated by human activity—appear to be making the greatest contributions to global climate change. Both gases are more abundant in the atmosphere than at any time during the preceding 400,000 years.<sup>2</sup> Solution of this inherently chemical problem will require major contributions by chemists and chemical engineers.

At one point it was assumed that the earth, its oceans and rivers, and its atmosphere were so vast or self-cleansing that we could discharge anything into them without damage to our planet. We now know this is not true. Currently, we must deal with toxic waste dumps, with smog, with acid rain that kills forests, and with pollution of rivers and the ocean by chemical discharges. How did this happen?

Part of the problem is simply the slow accumulation of materials released into the environment. Any single activity may seem small and harmless, but all such activities add up. The combustion of fossil fuels has long been recognized as a major source of air pollution. For example, burning petroleum components in gasoline and diesel engines of vehicles can lead to air pollution by emission of unburned hydrocarbons and sulfur and nitrogen oxides produced during the combustion process. When this was realized, fuels were refined differently to reduce sulfur content and vehicles were fitted with catalytic converters, designed by chemists and chemical engineers, to remove the hydrocarbons and nitrogen oxides from vehicle exhaust. The catalytic converter was introduced in the U.S. automotive industry and is now used worldwide, an excellent example of the beneficial global effects of chemical science and technology. Fuel efficiency was also increased, so less fossil fuel had to be burned per mile traveled. This has provided major improvements, but the real solution may come from a change to other forms of energy production for transportation, as described in Chapter 10.

The chemical process industries make a huge contribution to civilization, but they have the potential for environmental pollution. During the early growth of the industry, many chemical companies built their plants in river valleys. The plants used the river water and subsequently returned it to the river with water-soluble by-products, while they discharged gaseous by-products into the air. Water and air pollution were serious problems near these plants. In recent decades, chemical manufacturing has undergone a revolution. Almost all chemical manufacturers in the United States, and increasingly worldwide, subscribe to a program called Responsible Care.<sup>3</sup> In brief, it involves a pledge by the manufacturers to make only products that are harmless to the environment and to its living occupants, and by processes that are also environmentally and biologically benign.

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<sup>2</sup>*Climate Change Science: An Analysis of Some Key Questions*, National Research Council, National Academy Press, Washington, D.C., 2001.

<sup>3</sup><http://www.americanchemistry.com/>

Another important initiative is called green chemistry,<sup>4</sup> developed as part of efforts to reduce pollution at the source; it is defined as “the design of chemical products and processes that reduce or eliminate the use and generation of hazardous substances.”<sup>5</sup> Originated in the United States (where prestigious awards for accomplishments in this area are given annually), it is increasingly becoming a worldwide program.

Benign processes help make chemical plants into good neighbors, and their operators into good citizens, but the products themselves are now being examined with a new perspective. For example, DDT (invented by Paul Müller, who received a Nobel Prize in 1948 for this invention) was an effective insecticide that greatly reduced the occurrence of insect-borne diseases such as malaria. However, its widespread use caused problems, because it is too stable. DDT persists in the environment and enters the food chain, a phenomenon that led to the nearly complete elimination of DDT use after it was shown to interfere with bird reproduction. At one point it was believed that persistence was a good thing, since the insecticide would keep on working, but it is now recognized that persistent chemicals can accumulate in the environment and lead to new or unexpected problems.

A similar situation is found with the herbicides that help make agriculture more productive by controlling weeds. Advantages are now recognized for herbicides having limited persistence, lasting long enough to do the job and then harmlessly disappearing.

Persistence was also the unforeseen problem with the role of chlorofluorocarbons (CFCs) in degrading the earth’s ozone layer. CFCs were invented to replace toxic and dangerous gases (such as sulfur dioxide) that had been used as the working fluid for compressors in early refrigerators and air conditioners. Indeed, CFCs are so unreactive under normal conditions that they are quite harmless to humans and other living things. However, they are so stable that they diffuse throughout the atmosphere. When they reach the stratosphere—where the ozone layer is found—the greater intensity of high-energy radiation from the sun finally causes slow decomposition of the CFCs. This decomposition process produces chlorine atoms that catalyze the destruction of ozone in a chemical sequence that is now well understood. For elucidating these chemical processes in the stratosphere, Paul Crutzen, Mario Molina, and F. Sherwood Rowland received a Nobel Prize in 1995.

While the high stability and persistence of CFCs provided a major advantage for such applications as refrigeration and air conditioning, escape of the gases into the air has resulted in unacceptable changes in the upper atmosphere. The solution to the problem is to invent new relatives of CFCs that are adequate coolants but are less environmentally persistent. Chemists have indeed created such new substances, which are now replacing CFCs.

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<sup>4</sup><http://www.epa.gov/greenchemistry/index.htm>

<sup>5</sup><http://www.epa.gov/greenchemistry/whatis.htm>

## Green Chemistry

A common definition of green chemistry, which clearly encompasses considerable chemical engineering as well, is "the design, development and implementation of chemical processes and products to reduce or eliminate substances hazardous to human health and the environment," (P. T. Anastas and J. Warner, *Green Chemistry Theory and Practice*, Oxford University Press, Oxford, 1998). A more recent article expands this definition to twelve principles (M. Poliakoff, J. M. Fitzpatrick, T.R. Farren and P.T. Anastas, *Science*, 297, 807-810 (2002)).

1. It is better to prevent waste than to treat or clean up waste after it is formed.
2. Synthetic methods should be designed to maximize the incorporation of all materials in the process into the final product.
3. Wherever practicable, synthetic methodologies should be designed to use and generate substances that possess little or no toxicity to human health or the environment.
4. Chemical products should be designed to preserve efficacy of function while reducing toxicity.
5. The use of auxiliary substances (e.g., solvents, separation agents, and so forth) should be made unnecessary wherever possible, and innocuous when used.
6. Energy requirements should be recognized for their environmental and economic impacts and should be minimized. Synthetic methods should be conducted at ambient temperature and pressure.
7. A raw material or feedstock should be renewable, rather than depleting, whenever technically and economically practicable.
8. Unnecessary derivatization (blocking group, protection/deprotection, temporary modification of physical/chemical processes) should be avoided whenever possible.
9. Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.
10. Chemical products should be designed so that at the end of their function, they do not persist in the environment, and they break down into innocuous degradation products.
11. Analytical methodologies need to be developed further to allow for real-time in-process monitoring and control before the formation of hazardous substances.
12. Substances, and the form of a substance used in a chemical process, should be chosen so as to minimize the potential for chemical accidents, including releases, explosions, and fires.

Many of the problems that affect our environment are the result of unexpected effects that accompany an entirely reasonable intention. The effect of CFCs on the ozone layer is such a case. Chlorofluorocarbons seemed to be perfect—they were chemically stable and noncorrosive, and they were not at all toxic—as replacements for the earlier toxic refrigerants. But then the ozone effect was discovered. Similarly, DDT seemed to be a perfect insecticide—controlling mosquitoes and other insects that transmit disease—until its effect on birds was discovered. A more recent example is methyl tertiary-butyl ether (MTBE), a fuel additive that improves the performance of gasoline in automotive engines. Unfortunately, spillage and leakage from underground gasoline tanks has allowed MTBE to enter the ground water. This has led to concern about the biological effects of MTBE and a probable end to its use.

To prevent or at least minimize such problems, we must better understand the environment at all levels, including the fundamental chemical processes that affect it. We have learned the lesson that when assessing the fate of new products in the environment, we should not underestimate the potential of these to appear in unexpected places. The recognition, avoidance, or solution of complex environmental problems requires the expertise of a variety of science and engineering disciplines. Only then will it be possible to produce realistic evaluations of how new compounds will be distributed and will act in the ecosystem. In addition to chemistry and biochemistry, fields such as solution thermodynamics and transport phenomena in which many chemical engineers work, as well as earth sciences and environmental engineering, have crucial contributions to make.

Another environmental problem is the contamination of soil by heavy metals or organics. These soil-based contaminants can produce health hazards by release of volatile substances, contamination of groundwater, or accumulation of heavy metals by plants growing in the soil. Incineration has been used to treat soils heavily contaminated by organic materials, but this approach is expensive and may result in other environmental problems. The potential toxicity of contaminated soils is governed by a variety of factors; the factors that affect bioavailability of soil-bound contaminants or the movement of contaminants in subsurface fluids are not well understood. Close cooperation of chemists and chemical engineers will be needed to gain the necessary understanding.

One promising form of treatment is bioremediation. Microbes in the soil are capable of converting organic chemicals to other compounds, and in the ideal case to  $\text{CO}_2$  and  $\text{H}_2\text{O}$ , and some microbes have been found to convert heavy metals to complexes with reduced toxicity. Microbes can be harnessed through addition of nutrients, other chemicals, or specific microbes to enhance beneficial microbially mediated chemical reactions. However, the complex chemistry and biology of subsurface soil systems makes it difficult to achieve predictable responses. A much deeper knowledge of the interaction of the chemistry of the soil, fluid movement, and microbial physiology is an important challenge to making

bioremediation a fully practical technology. (see Chapter 7 for discussion of related matters).

A half-century ago, people were only beginning to understand the extent to which human activity could affect the environment, often in very negative ways. Many of the early problems of pollution were the result of chemical processes, and “chemistry” received the blame. But “chemistry” has also provided solutions, and dramatic improvements have occurred. No longer do industrial plants belch foul smoke into the atmosphere, and no longer do chemical plants discharge brown or orange sludge into nearby streams and rivers. These improvements have been implemented by chemists and chemical engineers, and they have been implemented in ways that often have provided economic benefits to the United States.

This chapter has focused on the chemistry of the earth and its immediate atmosphere, but the concept of “environment” need not stop with the earth’s atmosphere. Molecular chemistry also goes on in space, and it is an area of interesting chemical science. Large, although extremely diffuse, clouds of molecules exist between the stars, and such clouds are believed to be the origins of stars. So far, the chemistry in the clouds has been investigated not by direct sampling, but instead by observing the light that is emitted from them. Observations of such light in the microwave range have led to the identification of many remarkable substances—and of the likely transformations that they undergo. Chemists have synthesized some of these unusual substances here on earth so their microwave radiation can be compared with that from space, for identification of the space molecules. In addition, computational chemistry has reached the stage at which it is possible to predict the microwave radiation that some molecules would emit, again enabling earth-bound scientists to obtain evidence for the structures of materials that exist only in outer space.

## CHALLENGES AND OPPORTUNITIES FOR THE FUTURE

Considerable progress has been made in understanding the environment and the chemical processes that affect the environment. However, the preceding discussion clearly shows that many challenges remain. Chemical scientists must learn how to make useful substances that have limited persistence—and will generate only completely harmless products when they degrade.

A full understanding will be needed of the complex chemistry by which the atmosphere and the earth interact, including the dependence of global climate on carbon dioxide concentrations in the atmosphere. Is there a way to deal with the carbon dioxide produced by burning coal and other hydrocarbon fuels so that it causes no problem? Chemical scientists will need to investigate effective ways to trap  $\text{CO}_2$  that would otherwise build up in the atmosphere. Alternatively, it will be necessary to find ways to reduce the generation of carbon dioxide. As human

activity continues to destroy forests, will this affect the carbon dioxide cycle and levels, and what can be done about that?

### Supercritical Processing

Today we are witnessing a “green” revolution as it pertains to manufacturing industries’ implementation of carbon dioxide as a replacement for their dependency on water and organic solvent usage. A major impetus for this conversion is driven by a concern for our environment—to reduce a company’s footprint on our planet by reducing their usage of solvents and water. In addition, because of the low heat of vaporization of supercritical CO<sub>2</sub> (sCO<sub>2</sub>) relative to water and organic solvents, corporate motivations also include the reduction of energy usage associated with using CO<sub>2</sub>-based processes relative to conventional solvents and water. However, beyond pollution prevention and energy efficiency issues, sCO<sub>2</sub> is finding increasing appeal because of increased performance attributes associated with its inertness to many chemistries, to its exceedingly low surface tension and viscosity, and to its adjustable solvent quality due to its compressibility, especially in the supercritical state. Its critical temperature is conveniently located at 31°C, and it is both nontoxic and inexpensive. Recently, sCO<sub>2</sub> has been or is in the process of being commercialized in:

- Extraction processes for natural products including the decaffeination of coffee and tea and the isolation of nutraceuticals, flavors, and fragrances
- The production of melt processable plastics based on fluoroolefins
- The replacement of toxic solvents used in professional garment “dry” cleaning and critical/precision cleaning of manufactured goods
- Coating/encapsulation technologies for pharmaceuticals, textile apparel, and manufactured parts such as in the automotive industry
- Particle formation for use in drug delivery and xerography

These processes are enabled by breakthroughs in many areas. A fundamental understanding is emerging of the rational design of surfactants for sCO<sub>2</sub>—molecules that reversibly self-assemble as the density of compressible sCO<sub>2</sub> is adjusted. Such surfactants enable the stabilization of polymer colloids in sCO<sub>2</sub> for heterogeneous polymerizations and for the emulsification of numerous sCO<sub>2</sub>-insoluble substances including proteins, water, and catalysts to name a few. Creative engineering unit operations have been designed that allow for continuous reactions, automated reaction/separation schemes, and novel membrane-based separations. And finally, creative combinations of chemistry (novel compounds such as sCO<sub>2</sub>-soluble functional polymers) with sCO<sub>2</sub>-based applications have enabled entirely new processes.

Future commercial use of CO<sub>2</sub> will surely include such diverse applications as thin-film deposition for microelectronics using recently developed pressurized spin-coating and free meniscus coating instruments; in separations of value-added products from fermentation broths in biotechnology fields taking advantage of the immiscibility of CO<sub>2</sub> with water; and as the solvent in a broad range of synthesis including transition metal and enzymatic catalysis. All of these applications will lead to sustainable manufacturing methods that are not only ecologically preferable, but in themselves are enabled by working with a unique solvent that has the density of common liquids but the transport properties of a gas.

Humans affect the environment through simple living activities—they generate waste. Ordinary waste sites, in which people place trash and garbage, generate methane by microbiological action, and methane is one of the most potent greenhouse gases. Is this a significant problem, and if so, what can be done to prevent or solve it? Will it be possible to recycle waste that we currently bury, perhaps ameliorating the problem of waste sites? And if so, could we recover some of the chemicals and energy that were used to manufacture the discarded materials? Chemists and chemical engineers will need to devise the ways in which materials that are harvested from the earth can be recycled, not just discarded or burned. One of the approaches is bioremediation, in which microorganisms, perhaps genetically modified, are used to deal with the waste. This approach has already been used to some extent in dealing with oil spills. The ultimate goal is sustainability: using and recycling materials so that we do not simply exhaust the substances we have inherited, thus leaving less for our descendants.

The future production of chemicals will require continued awareness of possible unforeseen consequences, particularly with substances that persist in the environment. This will require investigation of how these substances interact with the environment, and it will necessitate the invention of new substances. As noted above, new and safe refrigerants will be needed that lack the persistence of CFCs. The world's food supply will depend on the discovery of new insecticides that do not harm unintended targets in any way and other agricultural chemicals such as herbicides and fertilizers that are neither harmful nor overly persistent. Other sectors of the chemical industry will rely on the invention of new and selective catalysts that enable the manufacture of useful products, including polymers, without producing unwanted waste products and without using excessive energy.

The existence of waste from past activities has created problems that will demand the attention of chemists and chemical engineers. Environmental cleanup—of toxic wastes, of contaminated groundwater, of radioactive waste—is a daunt-

ing challenge. Only by developing effective ways to clean up contaminated sites—and by developing processes by which such contamination can be prevented in the future—will it be possible to take full advantage of the technological opportunities that science has provided over the last century.

There are serious questions about the effect of continued growth of the human population. We often focus on the matter of adequate food production, but large populations also affect the environment and our need for energy. Chemists can furnish the tools to help deal with the political and social questions. Some population growth occurs not because it is intentional, but because adequate methods for birth control are unavailable to people in poor countries. Thus one challenge for chemists is to develop better methods that would be safe, effective, and inexpensive and would enable all people to pursue their own decisions regarding population growth.

Small amounts of some contaminants can be serious. When we burn coal, not only do we produce carbon dioxide, the major product, but we can liberate small amounts of mercury and larger amounts of sulfur dioxide. The mercury can form toxins that harm fish as well as humans, while sulfur dioxide can produce acid rain that destroys forests and water supplies. How can these contaminants be most effectively removed or dealt with? And how can we generate the energy that we need without releasing such by-products?

Environmentally responsible methods to manufacture useful products and to generate energy still need the largest contributions from chemists and chemical engineers. As we reexamine all human activities with a fresh eye, to see their environmental impact, the continuing challenge will be to invent new ways to achieve what society needs. Understanding the environmental effects of what we do is the first step, a job for basic chemical science. Inventing ways to improve what we do while still meeting human needs is a job for applied chemistry and chemical engineering. The opportunities for our science to improve the human condition will continue to pose exciting and important challenges.

Important educational challenges also confront the chemical sciences. Continuing emphasis on science education by government, foundations, industry, and educational institutions at all levels is essential. It is also essential to engage the professional practitioners in the chemical sciences—chemists and chemical engineers engaged in the broad spectrum of activities that characterize these fields—in education. Public outreach programs of professional societies like ACS and AIChE are important components, but more effort is needed both at the grassroots community level and in the improvement of the visibility of the chemical sciences through mass media. Greater emphasis in science and engineering education on the human aspects of the scientific endeavor is needed. Chemists and chemical engineers must also continue their own educations. This will improve their ability to contribute to a broader public understanding of science and technology, and it will enhance the contributions they can make to society.

We have come a long way. But there is still a long way to go. If we are to provide a favorable legacy for future generations, chemists and chemical engineers will need to develop effective ways to clean up existing waste and find ways to prevent the generation of waste in the future. And most importantly, they will need to develop a system that is fully sustainable—that will safely provide the energy, chemicals, materials, and manufactured products needed by society while neither irreversibly depleting the earth's scarce raw materials nor contaminating the earth with unhealthy by-products.

### WHY ALL THIS IS IMPORTANT

Human activity, including manufacturing, can damage our environment if we are not thoughtful and careful. We do not want to live on a planet where the air and water are dangerous to health, or where life is not possible for various plants and animals. In the past society did not worry enough about such questions, but now we have learned to take them seriously. Fortunately, it has turned out that environmentally benign chemical manufacturing, using the principles of Responsible Care, is both environmentally useful and economically acceptable. In fact, many companies have discovered that good environmental practices are actually cost effective. In any case, the challenge is to learn how to continue to develop a modern civilization without causing environmental damage.

The consequences of human action on the environment are not always completely foreseeable, so there is also the challenge to recognize the likelihood and magnitude of those consequences that we can foresee, and to recognize patterns of particular vulnerability. To meet this challenge it is essential that we continue to cultivate a strong base of fundamental knowledge in the chemical and biological sciences—for we will need those tools not only to create new technologies, but also to anticipate their consequences. We must approach the creation of science and technology for human advancement with intelligence, knowledge, and reason. That is, after all, what makes the human animal special.

# 10

## Energy: Providing for the Future<sup>1</sup>

### **Some Challenges for Chemists and Chemical Engineers**

- Develop more stable and less expensive materials and methods for the capture of solar energy and its conversion to energy or to useful products.
- Design inexpensive, high-energy-density, and quickly rechargeable storage batteries that make electric vehicles truly practical.
- Develop practical, less expensive, more stable fuel cells with improved membranes, catalysts, electrodes, and electrolytes.
- Develop materials, processes, and infrastructure for hydrogen generation, distribution, storage, and delivery of energy for vehicles.
- Develop photocatalytic systems with efficiencies great enough to use for chemical processing on a significant scale.
- Learn how to concentrate and securely deal with the radioactive waste products from nuclear energy plants.
- Develop practical superconducting materials for energy distribution over long distances.

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<sup>1</sup>As part of the overall project on Challenges for the Chemical Sciences in the 21st Century, a workshop on Energy and Transportation will lead to a separate report. The reader is urged to consult that report for further information.

- Develop technologies and catalysts for the cleaner use of coal as a fuel and for the conversion of coal to other fuels.
- Develop methods to use biomass as a renewable fuel source.
- Develop technologies for the improved extraction of conventional fossil fuels, including unconventional sources such as oil shale, tar sands, and deep-sea methane hydrates.
- Develop practical and environmentally responsible methods of carbon dioxide capture and sequestration.
- Develop lower cost, lighter weight, more durable, more resilient, and recyclable materials for the construction of safer lighter-weight vehicles.
- Develop improved materials, processes, and practices that will allow reduced energy use per unit of gross domestic product.

Chemistry and chemical engineering are intimately concerned with the generation and use of energy. We need energy for manufacturing, for transportation, for heating and cooling our homes, for lighting, and for cooking. Currently about 85% of the world's energy is obtained by burning fossil fuels—petroleum, natural gas, and coal—but this must change soon. Affordable supplies will become scarcer, and burning fossil fuels produces carbon dioxide that contributes to the greenhouse effect by which solar energy is trapped within the atmosphere and warms the planet. Burning fossil fuels, at least with current technology, also produces oxides of nitrogen and sulfur and other pollutants that affect plants and animals.

The problem of having enough clean energy is related to population, standard of living, and the efficiency with which energy is used to provide a unit of economic output. Humans will always need energy, and chemists and chemical engineers will continue to play a central role in learning how to produce and use it.

## GOALS

Chemists and chemical engineers will need to join with experts in other disciplines to invent new ways to generate and transport energy for human use and provide for the needs and aspirations of a growing population in a sustainable manner. New ways will also be needed to minimize the energy used for human activities, including manufacturing.

## PROGRESS TO DATE

### Generating Energy

Once petroleum is removed from the earth it is refined. It is separated into its various components by distillation, producing not only gasoline but also higher boiling materials such as diesel oil, kerosene, lubricating oil, and asphalt. Then part of it is *cracked*, converting some of the larger less volatile molecules to smaller ones more useful in gasoline, and it is *reformed*, transforming some of the molecules into others with smoother burning properties. Some of the products are also used as chemical raw materials, in addition to fuels.

Both cracking and reforming use special catalysts and processes. The overall process is highly efficient, so that essentially none of the components of petroleum are wasted. However, most agree that the supply of inexpensive petroleum will run out sometime, although there is disagreement as to exactly when. At current rates of consumption, we may still be using petroleum as a major source of energy 50 years from now. Natural gas may last 100 years, while coal reserves could last for perhaps four centuries. If population growth and standard of living improvement lead to increased energy consumption rates despite conservation efforts, the currently economically recoverable reserves will be depleted in a shorter period of time. In any event, development of more expensive fossil fuel sources—such as oil shale, tar sands, methane hydrates that are found at the high pressure of the deep sea, and coal, oil, and gas that current extraction technology leaves behind—will also be required.

Chemists and chemical engineers have developed processes for the gasification of coal, converting it by chemical transformation into *syngas*, a cleaner, more convenient energy source. They have also devised ways to convert coal into a liquid that can be used in place of gasoline in combustion engines. However, whether coal is used as a solid or converted to a liquid or gas, when it is burned the result is still carbon dioxide, a greenhouse gas.

Some chemical processes use energy directly to drive the transformation. For example, the conversion of iron ore, iron oxide, to iron metal requires chemical energy to remove the oxygen atoms. In early times the iron ore was heated with charcoal; in more recent times it is heated with refined coal (coke), but in both cases the result is conversion of coal or wood into carbon monoxide, which is toxic but can be burned to carbon dioxide to generate needed heat. There is now interest in devising processes that do not use carbon in this way, but use electrical energy to avoid the production of carbon oxides.

There is also interest in finding feasible and harmless ways to capture and permanently sequester carbon dioxide underground or in the oceans, thereby preventing its accumulation in the atmosphere.<sup>2</sup> Carbon dioxide concentration in the

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<sup>2</sup>*Carbon Management: Implications for R&D in the Chemical Sciences*, National Research Council, National Academy Press, Washington, D.C., 2001.

atmosphere has increased by about one-third since the beginning of the industrial revolution. Unless combustion of fossil fuels is halted, or unless carbon dioxide from fossil fuel burning is completely and permanently sequestered, carbon dioxide concentrations in the atmosphere will inevitably continue to rise with potentially significant consequences for global warming.

### **Alternatives to Fossil Fuels**

#### *Solar Energy*

Almost all of our energy has come from the sun. This is obvious when we burn wood, in which solar energy has been in a sense stored in a tree by photosynthesis. When whale oil was a significant fuel it was only a little more indirect—the whales ate plant material that was also produced by sunlight, and then converted that food energy into the energy in their oil. Petroleum, natural gas, and coal are also just stored forms of solar energy, from plants and animals that lived and were buried long ago, while hydroelectric and wind power are derived from more contemporary solar-driven oceanic evaporation and atmospheric pressure gradients.

In photosynthesis, plants convert carbon dioxide into oxygen of the air and carbonaceous materials of the plant; burning the plants simply sends the carbon back to carbon dioxide again. Thus the cycle—carbon dioxide plus light to form plant material and oxygen, then burning the plant material to consume the oxygen and regenerate carbon dioxide and liberate energy—is one way to capture the energy of the sun. The critical need is to avoid overloading the cycle, producing carbon dioxide faster than it can be recycled into plant material—a significant concern for current levels of fossil fuel combustion.

Although energy systems are currently dominated by fossil fuels, alternatives need to be developed. There is no obvious single solution, but a variety of approaches could make useful contributions. One plan would be to grow special grasses or other plants that are particularly efficient at converting sunlight into biomass (plant matter), then convert the biomass to electricity either by burning or by some version of a fuel cell. Genetic engineering may permit us to design new green plants that are particularly efficient at converting sunlight into useful fuels. Water and arable land would be needed for this scheme, but it is argued that we do not yet need all the arable land for the production of food and fiber. Another alternative would be to encourage the growth of phytoplankton in the ocean by intentional fertilization with limiting micronutrients such as iron. The process would serve as a mechanism for sequestering some carbon dioxide from the atmosphere; the resulting organic material would not be harvested as fuel but some instead would sink into the ocean depths before completing the cycle back into carbon dioxide. As with other proposals for carbon sequestration, there is no scientific consensus on its efficacy and safety.

Scientists, including chemists and chemical engineers, have also been pursuing the direct capture of solar energy, either for heating or for directly generating electricity.<sup>3</sup> One plan would cover significant amounts of arid desert and other surfaces such as rooftops with photovoltaic cells that directly convert solar energy into electricity. At the present time, photovoltaics can convert as much as 30% of the incident sunlight to electricity. The technical challenge, however, is to devise materials and manufacturing processes for photocells that are cheap, long lasting, and efficient in the conversion of light to electricity; ways are also needed to collect, store, and distribute the energy when and where it is needed. These problems have not yet been completely solved. A related advance is the invention of electrically conductive polymers, which are not metals. Alan J. Heeger, Alan G. MacDiarmid, and Hideki Shirakawa received a Nobel Prize in 2000 for opening up this important new area of science.

In an alternative way to take advantage of the sun's energy, photocells are under development using sunlight to drive chemical transformations, perhaps even producing chemicals that in turn could be used to generate electricity. For example, the photochemical generation of hydrogen, by splitting water, could be combined with a hydrogen fuel cell in this way. This area strongly depends on basic research in photochemistry.

### *Nuclear Energy*

An alternative to solar energy is provided by nuclear energy—currently the source of 7% of the world's total energy and 20% of U.S. electrical energy. Chemists and chemical engineers have devised the processes for producing the nuclear fuels from crude uranium ores. In many countries nuclear power plants are major sources of electricity (as much as 75% in France), but one of the problems is nuclear waste. A typical nuclear energy plant produces 20 metric tons of radioactive waste each year. Chemists and chemical engineers are working to devise methods to separate the radioactive material from the inert material in which it is produced. If this is successful the volume of radioactive substances to be handled will be much less, and some of the purified radioactive materials may be available for other uses (including medical diagnostics and treatment). As another approach, converting the waste products to tough ceramics could make them stable for very long periods of time. The development of safe methods for dealing with radioactive waste—together with public acceptance of them—pose a challenge to which chemists and chemical engineers can respond.<sup>4</sup>

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<sup>3</sup>For further discussion of this topic, see ref. 1 and ref. 2.

<sup>4</sup>See for example: *Electrometallurgical Techniques for DOE Spent Fuel Treatment: Final Report*, National Research Council, National Academy Press, Washington, D.C., 2000; *Alternatives for High-Level Waste Salt Processing at the Savannah River Site*, National Research Council, National Academy Press, Washington, D.C., 2000.

Nuclear energy offers many advantages if the waste problem can be solved. The fuel is inexpensive, the energy can be generated near where it is to be used, and there are no greenhouse or acid rain effects. Of course, a special problem with nuclear energy is the hazard if the plant is run carelessly, and it is possible that the operation of a nuclear power plant could be diverted to develop material for nuclear weapons or the radioactive by-products could be used in terrorist attacks. However, it is important to solve these problems so that the currently negative public perception of nuclear energy undergoes a change, and permits nuclear energy to make its full possible contribution to the world, particularly after we have stopped burning fossil fuels.

Whether nuclear power generation increases as a contributor to our energy supply or merely continues on its present course, the aging population of nuclear chemists and engineers poses a significant concern. There has been a steady reduction in the number of university programs in nuclear chemistry, radiochemistry, and nuclear engineering—and in the number of graduates they produce.<sup>5</sup> Unless a new pool of expertise is developed, it will become increasingly difficult to safely operate existing reactors, manage the radioactive waste that will be produced (along with that which already exists), and clean up radioactive contamination from earlier activities.

### *Water and Wind*

Approximately 10% of U.S. electrical energy is produced by hydroelectric dams.<sup>6</sup> Although there are few economic and environmentally acceptable dam sites remaining, in some places it is possible to use wind power, or perhaps even the ocean tides, to generate electricity. Here the opportunity for chemists and chemical engineers is the invention and production of modern materials that can make such approaches possible.

## **Energy Efficiency, Conversion, Storage, and Distribution**

In recent years, much attention has been devoted to improving the efficiency with which energy is produced and used by society in general and also in chemical manufacturing. Higher fuel efficiency in automobiles, better insulation materials and construction practices for homes, and energy efficient lighting and ap-

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<sup>5</sup>*Nuclear Education and Training: Cause for Concern?* The Nuclear Energy Agency, Organisation for Economic Co-operation and Development (OECD), Paris, 2000 [<http://www.nea.fr/html/ndd/reports/2000/nea2428-education.pdf>]; *Training Requirements for Chemists in Nuclear Medicine, Nuclear Industry, and Related Areas*, Report of a Workshop, National Research Council, National Academy Press, Washington, D.C., 1988.

<sup>6</sup>*Renewable Power Pathways: A Review of The U.S. Department of Energy's Renewable Energy Programs*, National Research Council, National Academy Press, Washington, D.C., 2000, p. 116.

pliances are familiar examples. Internal combustion-electric hybrid vehicles are another area in which multidisciplinary science and engineering research is striving to produce extremely efficient, if perhaps not yet economically practical, transportation systems. For electrical power generation, complex systems such as coal-gasification combined-cycle and natural gas combined-cycle are being installed to reduce the amount of carbon dioxide produced per unit of electricity generated. A combined-cycle generator increases efficiency by capturing heat from the gas-turbine exhaust stream and produces additional power with a steam turbine. As a consequence of electricity deregulation, various heat and power cogeneration and distributed power generation schemes with micro turbines or fuel cells are also being explored. Again, contributions by chemists and chemical engineers will be critical, especially in the development of high-temperature and other advanced materials.

### *Electrochemical Cells*

Instead of burning fuels such as petroleum or coal or natural gas to produce steam for electrical turbines, electrochemistry can be used to generate electricity directly from chemical reactions—thus avoiding the waste of energy and the pollution that comes from combustion. This approach is particularly attractive for use in portable energy sources and vehicles. A common example of such an electrochemical cell is an old-style flashlight battery that cannot be recharged. In such a battery, a metal such as zinc gives up electrons as it is oxidized to a zinc ion, while another material such as manganese dioxide is reduced by those electrons to form manganese ions. The battery is constructed with separators or membranes in such a way that the electrons from the zinc must travel outside the battery through an external circuit before returning to the battery to reduce the manganese dioxide. In this way electricity is used directly. The zinc metal and the manganese dioxide were both originally made in a factory by oxidation-reduction reactions of zinc salts and from manganese salts, so the battery represents a convenient way to store and deliver electricity.

Batteries have been developed from many pairs of chemicals capable of being oxidized and reduced. Some systems are rechargeable; after the chemicals in the battery have been exhausted, the reactions can be reversed by the application of an external source of electricity. The lead-acid automobile battery is a familiar example. In many applications, such as cell phones and laptop computers, the weight of a portable electricity supply is critical. This has led to the development of batteries based on lightweight lithium chemistry, for which challenges still remain.

Electrochemists have also learned how to make electrochemical cells in which one of the reactants is continuously supplied from outside the cell rather than contained within. One example is the zinc-air cell in which particles of zinc

metal contained in the cell react with the oxygen of the air brought in from outside the cell to make zinc oxide, again with the generation of electricity. One can imagine a scenario in which such a cell could replace the petroleum-fueled engine of an automobile. The vehicle would be driven by an electric motor with the electricity supplied from a zinc-air cell. When all the zinc had been oxidized, a "service station" would remove the part of the cell with the zinc oxide and replace it with a fresh supply of zinc metal. The station would return the zinc oxide to a factory where electricity would be used to convert it back to zinc metal.

### *Fuel Cells*

Electrochemical cells in which *both* reactants are continuously supplied from outside the cell, particularly those in which the reactants are oxygen and an otherwise combustible fuel, are generally referred to as fuel cells. Chemists and chemical engineers have devised a large number of fuel cells that differ in the reactants used, as well as in the separators, electrolytes, catalysts, operating temperatures, and other construction details. One example uses hydrogen and air. The cell reaction converts hydrogen fuel and the oxygen from the air to water, just as if the hydrogen were being burned. But this process generates electricity directly with a greater energy efficiency than that obtained from a process such as burning the hydrogen in a combustion turbine generator. A hydrogen fuel cell also operates in a cycle. The reaction of hydrogen and oxygen in the fuel cell to produce water is one part of the cycle. Elsewhere, a source of electricity could be used to electrolyze water and generate hydrogen and oxygen. The net result is to move energy from an electrical generating plant to a remote fuel cell.

A fuel cell avoids the production of nitrogen oxide pollutants that are generally formed in combustion processes. Nitrogen oxides formed during generation of the energy needed for production of hydrogen (or other fuel) can be removed by scrubbing the exhaust gases in the generating plant. Hydrogen fuel cells were first used in the space program (with pure oxygen rather than air), but they are being developed for a variety of terrestrial applications that range from portable electronics, to vehicles, to back-up emergency power systems.

There are still many unsolved problems for hydrogen fuel cells. One is the rate of reaction of the oxygen at the electrodes, which is not yet as rapid as desired. Related to this is the high cost of current membrane and catalyst systems. Another unsolved problem is how to transport and store hydrogen safely for use with the fuel cell. For space applications, hydrogen has been stored as a cryogenic liquid. For terrestrial applications, one approach is to store the hydrogen as a very high-pressure gas in very strong lightweight cylinders made of advanced composite materials. Chemists and engineers are working on other approaches, such as adsorbing the hydrogen on carbon or spongy nickel, or as metal hydrides that can be stored safely at low pressure. But this and related problems have not yet

been solved. When they are, we could have what has been called the “hydrogen economy.”

In another version of a fuel cell, a carbon compound such as methanol (from natural gas or from the reaction of coal with water) reacts directly in an electrochemical cell with the oxygen in air to form water and carbon dioxide. This approach has fewer problems with storage of the fuel, and it has higher efficiency than power production from combustion of the same fuel—but it still produces carbon dioxide with its contribution to global warming. The performance of current fuel-cell catalysts may be degraded by carbon monoxide, an intermediate in the reaction with carbon-based fuels. In yet another variant, a hydrocarbon is caused to react with water in a separate device called a reformer to produce hydrogen along with a mixture of carbon monoxide and carbon dioxide; after separation, the hydrogen can be fed to a conventional hydrogen fuel cell. This approach avoids carbon monoxide degradation of the fuel cell performance, but it still produces carbon dioxide.

Although there is still much to do to make fuel cells widely practical, experimental automobiles have recently been exhibited that are powered by fuel cells. Thus there is every reason to expect fuel cells to play a major role in electricity production in the future.

### *Storage Batteries*

In the above scenarios the energy to produce the reactants for a battery or fuel cell was supplied in a factory, but another possibility is a storage battery that can be easily and quickly recharged either at a service station or at home. The familiar lead/acid car battery is an example, but it is not good enough to replace combustion of gasoline as the main power source in typical transportation vehicles. The batteries are too heavy and take too long to recharge.

What is needed is a high-capacity storage battery that is lightweight, inexpensive, long lasting, and rechargeable. The batteries now used in golf carts and in some recent electric automobiles do not meet all these criteria, but there is active research by chemists and chemical engineers to develop such batteries. When they exist, drivers will be able to stop at a service station and recharge their batteries in 10 to 15 minutes, then drive on for another 300 miles before a recharge is needed. In another scenario, the drivers might simply trade in their depleted batteries for others that have been recharged by a service station. When the problems are solved, we will be able to reduce our dependence on petroleum-fueled automotive engines.

We also use small rechargeable batteries to power cell phones and portable computers. They are reasonably light and have the capacity to go for some hours before requiring recharging, but improvements are still needed. As chemists and chemical engineers develop better battery technology we can expect to be freed

from the need to recharge the batteries in our computers or cell phones quite so often.

### *Energy Distribution*

Portable energy is important for vehicles and small electronic objects such as cell phones, but we also need to distribute energy from the generating plant to the place where it is to be used. Whether it is generated using photocells in the desert, by growing biomass in agricultural areas, or by operating nuclear power plants, it must go from there to the manufacturing plants and homes where it is needed. Currently this is done with power lines made of ordinary conducting materials such as copper or aluminum, but the electrical resistance of those metals results in considerable loss of energy. Thus there is great interest among chemical scientists in developing practical superconducting materials for power distribution.

Superconductors pass electricity with no resistive loss, but so far they operate only at extremely low temperatures, and are impractical for power distribution. However, as the basic science of materials progresses it is hoped that eventually superconductors will become practical for operation closer to normal temperatures while carrying a large current flow. This is a particularly difficult challenge, but if it can be met, the rewards will be enormous. There is already progress—superconducting power cables that can operate when cooled by liquid nitrogen are being made for short-distance power distribution in some urban areas.

The approach described above involves the idea that there is a central power plant from which electricity is distributed, but there is another choice. It might be possible to distribute the power generation itself, having small generators locally sited where the power is used. Already many large buildings have their own power generators (as do some private homes), although these are primarily for emergency use. This distributed approach offers the advantage that power is generated locally and only when needed, so energy losses from transmission would not cause problems. For this approach, fuel cells may have an important role if they become practical and can operate using locally available fuels.

## **CHALLENGES AND OPPORTUNITIES FOR THE FUTURE**

A variety of opportunities and challenges have been described in the preceding section along with an indication of where current progress is inadequate. We must eventually learn how to operate in a world that is not energized by burning fossil fuels, and the opportunities and challenges are clear. In the meantime, while we are still burning coal and hydrocarbons, we need to learn how to deal with the carbon dioxide that is produced. This must be done to address the problem of global climate change and to eliminate the environmentally harmful side products of combustion. We need to devise better ways to use solar energy, for ex-

ample by creating practical cells for conversion of sunlight to electricity. We need to replace combustion by fuel cell technology, and we need to solve the problem of how to transport and store hydrogen. We need to invent rechargeable batteries that are practical for vehicles that have electric motors instead of gasoline engines. Advances in both basic and applied chemistry and chemical engineering are needed to achieve these goals.

### **WHY ALL THIS IS IMPORTANT**

The challenges and opportunities in the field of energy are critical for a world in which inexpensive, readily available fossil fuels will eventually be exhausted. Unless we learn how to generate and store energy, not just burn up the fuels formed in earlier times, we will be unable to continue to advance the human condition or even maintain it at its current level. The problems are of central importance, but they can be solved—and the chemical sciences are a necessary part of the solution.

## National and Personal Security<sup>1</sup>

### **Some Challenges for Chemists and Chemical Engineers**

- Invent strong, lightweight, and multipurpose materials for military use in vehicles, armaments, and protective clothing.
- Devise ways to detect mines, both on land and in the sea.
- Develop robust and reliable sensors for detection of chemical agents, biological agents, radioactive materials, and explosives.
- Develop portable miniaturized analytical devices for personal protection or remote deployment.
- Develop effective ways for mitigation of chemical, radiological, and biological terrorist attacks, and devise ways to decontaminate the sites of such attacks.
- Invent effective antivirals and antibiotics for response to attacks with biological agents.
- Invent ways to detect dangerous materials in our food or water, and to detoxify them.

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<sup>1</sup>As part of the overall project on Challenges for the Chemical Sciences in the 21st Century, a workshop on National Security and Homeland Defense has led to a separate report: *Challenges for the Chemical Sciences in the 21st Century: National Security & Homeland Defense*, National Research Council, National Academies Press, Washington, D.C., 2002. The reader is urged to consult that report for further information.

Science and technology have always played a major role in national security, particularly to arm and protect our military forces. The September 11, 2001, attack on our country has directed tremendous attention to science and technology and ways that it might be mobilized for national security and homeland defense. The very real threat of future acts of catastrophic terrorism has become a significant force for shaping research directions in chemistry and chemical engineering. The most critical needs for national security are inherently chemical capabilities, such as the means to analyze and detect threats by providing intelligence and warning, and the ability to respond to an attack by mitigating damage and decontaminating a site. Achieving these goals will require concerted basic and applied research in chemistry and chemical engineering.

The personal security of our citizens also benefits directly from science and technology. Our police forces are equipped with light, strong bulletproof vests made of modern synthetic materials, and fire rescue personnel wear protective clothing made from temperature-resistant polymers. The smoke detectors and carbon monoxide detectors in our homes are based on chemical processes that detect dangerous substances. Personal security is enhanced in the broadest sense by water purification and by the chemical testing procedures that assure us of clean water and food.

## GOALS

Chemical science and technology must contribute to the enhancement of national and personal security by providing fundamental understanding and new developments—to defend against military, terrorist, or criminal attack and to give warning of accidental or natural disasters. Chemists and chemical engineers will need to make new discoveries in basic science and apply them to the creation of useful materials and devices. These activities will need to address the threats to both military personnel and the civilian population. The range of threats in turn will include military or terrorist attacks on a massive scale, other assaults against just a few individuals, natural disasters, industrial accidents, transportation-related mishaps, and accidents in the home. The goals, to which chemical scientists can contribute, begin with early detection and prevention of an attack or event—but if prevention is not possible, they extend to mitigation of the effects and subsequent remediation of damage.

## PROGRESS TO DATE

### Military

Ever since World War II spurred the development of technological advances such as radar, synthetic antimalarials, and synthetic rubber, our nation's strengths

in science and technology have enabled us to prevail in the battlefield and marketplace. The United States currently has a military equipped with materials, communication devices, and supplies that result from fundamental research in materials synthesis and processing, electronics development, and biomedical advances.

Nuclear weapons, frightening and dangerous as they may be, are nevertheless a significant component of our overall national defense. A major national effort at this point is to make sure that they are not used in a war, or allowed to spread into less responsible hands. Chemistry played a large role in the development of nuclear weapons, enabling the chemical and isotopic separations procedures by which weapons-grade fissile materials could be isolated from highly complex mixtures. It was a remarkable achievement, solving a very difficult problem. Now analytical chemistry is heavily involved in detecting evidence for nuclear test explosions, to try to prevent the proliferation of nuclear weapons.

The production of weapons-grade uranium or plutonium is both technically challenging and expensive. Consequently, the source of this threat has been limited primarily to industrialized countries. In contrast, both industrialized and less developed countries might turn to the production of chemical weapons or biological weapons using dangerous viruses or bacteria. These are forbidden by international agreement,<sup>2</sup> but agreements do not necessarily provide a strong defense. Consequently, the U.S. military has put considerable effort into developing protective clothing and procedures to protect troops against chemical and biological weapons. The protective materials, and detoxifying procedures and substances, are the products of modern chemistry and chemical engineering.

A major contribution from chemistry and chemical engineering has been the development of materials with important military applications. Chemists and chemical engineers, working with experts from areas such as electronics, materials science, and physics, have contributed to such developments as new explosives and propellants, reactive armor (a complex material with an explosive layer that can reduce the penetration of an incoming projectile), and stealth materials that reduce the detectability of aircraft by radar.

### Personal Security

Our personal civilian security is greatly enhanced by many contributions from chemistry and chemical engineering, often through integrated R&D efforts with teams of scientists from many disciplines. Law enforcement employs forensic tools that rely heavily on chemical analysis, and emergency response teams use a variety of protective clothing and equipment that rely on modern materials chemistry and engineering. As mentioned above, individual security extends to chemical detection methods in the home.

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<sup>2</sup>The Biological and Toxin Weapons Convention, <http://projects.sipri.se/cbw/docs/bw-btwc-mainpage.html>; the Chemical Weapons Convention, <http://www.opcw.nl/>.

## CHALLENGES AND OPPORTUNITIES FOR THE FUTURE

### Military

New research is needed to equip our military for new types of combat in diverse environments, and against well-equipped opponents. Increasingly, combat may occur in difficult areas, such as jungles or cities. These new situations require that soldiers be independent agents who are able to carry their weapons, communications, and supplies. Chemical scientists need to develop lightweight strong materials that could replace the heavy metal armor in fighting vehicles; new ultratough composites are a likely choice. Other lightweight materials will be needed for surveillance vehicles and to equip rapid response forces. Military vehicles will need better batteries and fuel cells to provide portable energy sources (Chapter 10).

The materials for uniforms and equipment will need to provide protection from chemical and biological agents (and perhaps detect them as well), be lightweight, and provide climate control to maintain performance in extreme environments. New medicines—antivirals, antibiotics, and antifungals—will be needed to maintain the health of troops deployed in such locations. In urban areas, advanced materials are needed for robots that can enter buildings before soldiers.

Combat medicine poses special problems. Chemical science and technology can aid in the rapid detection and treatment of injuries from chemical and biological weapons and other new weapons such as lasers. We need to develop blood substitutes with a long shelf life, and improved biocompatible materials for dealing with wounds. For the Navy, there are special needs such as analytical systems that can sample the seawater to detect and identify other vessels. We need good ways to detect mines, both at sea and on land. Land mines present a continued threat to civilians after hostilities have ended, and chemical techniques are needed to detect these explosive devices.

Of course our national security also depends on deterring problems before they arise. We need to develop new analytical chemistry techniques that are capable of detecting the production of materials in violation of the chemical and biological weapons treaties. Related detection technologies are needed to detect chemical agents and warn personnel accordingly. The new instrumentation will need to be versatile, robust, and portable—with miniaturization using approaches such as microfluidics as a likely goal.

### *Biological*

Biological warfare agents present a greatly increased threat because the original viruses or bacteria can multiply and infect additional people. Considerable concern has been expressed over the possibility that a terrorist group might obtain a sample of the smallpox virus. Until recently, it was believed that smallpox had

been eradicated, with the exception of samples at two specialized facilities (in the United States and Russia). Other biological agents also create concern. For example, *bacillus anthracis* (anthrax) has long been viewed as a potential weapon because it can be converted to hardy spores for delivery as a dry powder. The events of 2001 showed anthrax to be a dangerous organism, but it is not transmitted from one human to another. Consequently, the death toll from anthrax-containing letters was relatively low, although the societal and psychological impact was huge.

How can chemists and chemical engineers respond? To guard against biological attacks, it will be necessary to develop rapid and reliable methods of detection. As the events of 2001 demonstrated, it is not acceptable to culture a sample and wait days to learn if a particular biological agent is present; it must be identified prior to the onset of symptoms. And if the agent is found, we will need new therapies (antivirals, antibiotics) and reliable methods for decontaminating the site of attack. Protection of personnel will also require new vaccines and new approaches for delivering drugs and vaccines. The development of new drugs and vaccines will need to be carried out in full recognition that genetically modified pathogens could be used in an enemy attack. All of this will require concerted research by chemists and chemical engineers in collaboration with other scientists; these studies necessarily will be interdisciplinary.

### *Chemical*

Chemical warfare agents are extremely toxic and very fast acting. Chemical scientists must develop better understanding of their mechanisms of action, and use this information to devise possible remedies. At present, the logical response to the chemical threat is prevention of exposure. Consequently, sensors and other fast analytical techniques must be developed. Rapid and reliable methods of decontamination are needed in the event that a chemical agent is detected. One concept, the “lab on a chip,” involves producing complete analytical systems in a compact electronic form; such small devices could then be deployed by airdrop and allow remote inspection. Such miniaturized analytical systems also could be carried by individual soldiers—providing them with individualized real-time detection capability for chemical and biological agents.

The chemical industry is an important part of the U.S. economy. The manufacturing sites, and the chemicals they make, store, and transport, represent targets for terrorist attack—either by causing a release of toxic chemicals or by diversion of chemicals for other purposes. The industry needs to be sure that it has broad up-to-date information from analyses and risk assessments of chemical plant safety, of site security, and of chemical transport security. These analyses need to be coupled with detection capabilities for response, verification and tracking. Even with good plans in place, appropriate procedures are also essential for dealing with any attacks. Chemists and chemical engineers will be challenged to

develop new products and processes that make the chemical industry inherently more secure. Once again, mitigation and decontamination procedures require the attention of chemists and engineers.

### *Nuclear and Radiological*

Countries and groups that lack access to nuclear weapons may still have opportunities to obtain radioactive materials such as spent nuclear fuel. A bomb in which a conventional explosive charge causes dispersal of radioactive material is known as a “dirty bomb.” Such a device could result in psychological effects exceeding the physical damage it caused. Once again, new techniques are needed for detection (of both the explosive and radioactive material), and decontamination procedures would be essential if such a device were used.

Research by chemists and chemical engineers will be needed for the development of new analytical techniques to detect nuclear proliferation threats and treaty violations. This will require establishing the characteristic signatures of both production and testing of weapons. Detection of these signatures will depend on chemical spectroscopy techniques, and advances in remote sensing.

Within the context of the U.S. weapons programs, the ban on testing nuclear weapons requires that other methods be developed to ensure the safety and reliability of existing weapons. As part of the stockpile stewardship program, it will be necessary to understand—through laboratory experiments and via computer simulation and modeling—the long-term changes that could affect the performance of the weapons in the stockpile. These include chemical effects such as corrosion as well as the results of self-irradiation on both nuclear and nonnuclear components of the weapons. What are the aging processes and their consequences on various components—including high explosives, electronics, and mechanical—and how will this affect performance? Successful modeling will require fundamental understanding of materials over all length scales and of their chemical behavior under extremes of temperature and pressure.

### *Explosives*

Bombings have long been a central threat from terrorism, and several major bombing attacks have been carried out in the United States over the last decade. Two earlier reports from the National Research Council outlined a number of opportunities for technical contributions by chemical scientists.<sup>3</sup> The recommen-

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<sup>3</sup>*Containing the Threat of Illegal Bombings: An Integrated National Strategy for Marking, Tagging, Rendering Inert, and Licensing Explosives and Their Precursors*, National Research Council, National Academy Press, Washington, D.C., 1998; *Black and Smokeless Powders: Technologies for Finding Bombs and the Bomb Makers*, National Research Council, National Academy Press, Washington, D.C., 1998.

dations in those reports emphasized further research to develop new and improved detection techniques, but new voluntary and regulatory approaches to controlling explosives and their precursor chemicals were suggested if the level of threat increases.

### *Root Causes*

One of many underlying problems leading to conflict is the difference in standard of living between industrialized and developing countries.<sup>4</sup> Much of this difference could be mitigated by technology to improve energy, information infrastructure, medicine and public health infrastructure, food, water, shelter, clothing, and other absolute necessities for poorer nations. A task for chemistry and chemical engineering is to improve the means to feed and shelter the world, to extend to less-wealthy nations some fraction of the benefits we enjoy.

### **Personal Security**

In most respects, the terrorist threats to civilian populations are parallel to the military threats from chemical and biological agents, radiological materials, and explosives. Detection—with all its challenges to the chemical sciences—remains the key. But the response must be quite different if an attack takes place on a civilian target. In such a case, we would not be looking at a specific concentration of troops under management of senior military officers—whose goal must be a sufficient survival level that will enable the battle to be continued and won. In a civilian situation, reduction of casualties must take first priority.

Important opportunities in the area of response are found in the early stages of emergency response. Emergency personnel need improved materials—including clothing, gas masks, and gloves—for personal protection. These will need to be lightweight and long-lasting, with significant improvements over the current generation of protection suits that are too heavy, too hot, and too cumbersome.

The time scale for chemical and biological attacks is quite different. Explosives and chemical warfare agents such as nerve gases kill in seconds or minutes, but even the existence of a biological attack might not be recognized for days or weeks. The first responders in a chemical or explosive attack will be alerted by damage and casualties, and they will need to enter the disaster zone. They will need the appropriate protective gear along with the detection equipment to tell them what threat or agent(s) they are facing. Moreover, they will need equipment and chemicals that will allow them to decontaminate the site by destroying or removing whatever harmful agents may be present. Finally, their analytical equip-

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<sup>4</sup>*Discouraging Terrorism: Some Implications of 9/11*, National Research Council, National Academy Press, Washington, D.C., 2002, p. 29.

ment will need the sensitivity and accuracy to tell them when decontamination has progressed adequately so that the disaster zone can again be declared safe. All of the new equipment and instrumentation will require the work of chemists and chemical engineers.

Biological attacks will likely be recognized not from a summons to the site of attack but by the steady accumulation of unusual data collected by medical personnel at hospital emergency rooms. Only when the collated data are properly interpreted will the biological attack be recognized as such. But then it will be necessary to engage our medical and public health systems quickly. To be ready for such an event, chemists and chemical engineers will need to carry out extensive work in collaboration with others in the biomedical field. It will be necessary to develop new and better vaccines, antivirals, and antibiotics. Better, faster ways of making and delivering these materials will have to be developed so that they are available in time to save lives. If a biological attack should take place, improved detection methods for biological agents will be needed immediately. A rapid, accurate, and reliable method is needed for detecting and identifying infected individuals before clinical symptoms appear. Many biological warfare agents produce conditions that are curable only if treated prior to the appearance of clinical symptoms. Waiting for the symptoms of a lethal disease to appear will not be an acceptable alternative. Chemists and chemical engineers will need to develop sensors, instruments, and analytical procedures to identify pathogens rapidly and reliably—thereby enabling medical personnel to respond accordingly.

Protection of our food and water supplies against terrorist attack presents a major challenge, because the supply chain is so extensive and open. But it is a challenge that chemists and chemical engineers should accept. Moreover, the threats to food and water are not limited to terrorism—a variety of natural disasters could wreak havoc as well.

### WHY ALL THIS IS IMPORTANT

A compelling sense of urgency was felt throughout the United States after the terrorist attacks of September 2001. For chemists and chemical engineers, this has emerged as motivation to align their research directions in ways that can help deter terrorism and protect our country from attack. Chemistry and chemical engineering have major roles to play in furthering our defensive capabilities against both military opponents and terrorists.

All of the areas of research discussed in this chapter will require interdisciplinary collaborations among chemists, engineers, biologists, physicists, and materials scientists. This critical area of national need should be the catalyst for breaking down disciplinary barriers and promoting interaction among scientific and engineering communities.

Among the many areas of research that can contribute to our national security, several stand out from the rest as central to the chemical sciences—materi-

als, medicines, and sensors. Advanced materials will play a crucial role in military and civilian protection, and advanced research in structured and functional materials on a nanoscopic scale will be an important focus for chemists and chemical engineers. The very real threat of virulent biological agents will drive chemists, biochemists, and chemical engineers to seek new prophylactic treatments, therapies, and protective vaccines. The need to protect millions of civilians in our own communities against acts of catastrophic terrorism must be a central priority for those working with analytical sensors and detectors, and for those working with genomics and analysis of pathogenesis. There cannot be many more important goals.

## How to Achieve These Goals

U.S. prosperity depends on high technology, and much of that depends on chemical expertise. For most of the past decade, the chemical industry has been one of the few U.S. manufacturing industries to have a positive balance of trade. Indeed, the chemical process industries, which perform chemical transformations in the course of manufacturing their products, are as much as one-third of the entire U.S. manufacturing sector in terms of value added. The scope of the chemical sciences endeavor is vast, contributing far beyond the traditional aspects of chemistry and chemical engineering. As a consequence, opportunities for fundamental and creative science—and major contributions to technology and society—will remain in the hands of chemical scientists for a long time. New fundamental chemical insights will increase our scientific understanding, and the practical importance of future discoveries will have enormous potential. These new discoveries—medicines to cure and prevent diseases, solutions to meet our energy needs, paradigm shifts in electronic materials, increased industrial sustainability, and protection from terrorist attacks—all require the efforts of chemists and chemical engineers. The health and well-being of the chemical enterprise will directly affect the health and well-being of our nation and its economy.<sup>1</sup>

If these achievements are to occur, however, it will not be by the work of chemists and chemical engineers acting alone. Many parts of society and experts in other areas of science and technology will be partners with chemists and chemi-

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<sup>1</sup>*Chemical & Engineering News*, 78 (41), 60-61, 2000; *Chemical & Engineering News*, 79 (46), 38-39, 2001; *Chemistry Today and Tomorrow: The Central, Useful, and Creative Science*, Ronald Breslow, American Chemical Society, Washington, D.C., 1997.

cal engineers if the chemical sciences are to achieve solutions to all these challenges. The following section suggests opportunities for the path forward.

## CHEMISTS AND CHEMICAL ENGINEERS

### The Practice of Chemistry and Chemical Engineering

Future research for chemical scientists will increasingly involve working in multidisciplinary teams. This means not just analytical chemists with inorganic chemists or chemists with chemical engineers, but chemical scientists working with physicists and electrical engineers to develop electronic materials and devices, chemical scientists working with biologists and physicians in the development of medicines and the understanding of life processes, chemical engineers working with physicians to develop artificial materials and organs for the body, and chemical scientists working with business leaders and resource managers to develop sustainable and profitable processes for our world.

The need for multidisciplinary teams to understand the fundamental science of the future as well as to address the technical challenges ahead will require a shift in the way we train graduate students, award tenure, and fund research. It is desirable that graduate students be involved in projects that include other disciplines, and their classwork should involve a broader array of subjects than just their primary specialty. Tenure has traditionally been built upon individual research. Perhaps a demonstrated ability to collaborate with those in other disciplines should be considered a strong asset for tenure. To truly foster collaborative research, funding agencies need to provide awards that are larger than the present awards that are expected to fund only one principal investigator.

Besides doing multidisciplinary research, chemical scientists in the coming years will need to team with those from other sectors. Government and academe need to work together in order to most effectively solve the problems facing the nation in homeland defense and security. Industry and academia need to work together to enhance the transfer of technology to the marketplace and to keep academe in touch with the needs of industry. Government and industry need to team to better address the problems they face together.<sup>2</sup>

### The Training of Chemists and Chemical Engineers

As in any reexamination of the field, chemists and chemical engineers should ask serious questions about current practices. Does the divisional structure in academic chemistry departments discourage multi-investigator research, or encourage artificial distinctions? Are the traditional divisions still the best structure

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<sup>2</sup>*Research Teams and Partnerships: Trends in the Chemical Sciences*, National Research Council, National Academy Press, Washington, D.C., 1999.

for educating students or do these divisions encourage narrowness? Is it reasonable that the traditional education of chemists involves no contact with the field of chemical engineering? Since most chemical engineers are no longer doing research in areas related to the undergraduate classes that they teach, what does that imply about the need for changing the chemical engineering curriculum? These are all areas that will be debated and acted on in the near future.<sup>3</sup>

Regarding undergraduate education, most students are exposed to chemistry courses because they are considering careers in the health sciences. These introductory courses are an opportunity and responsibility to convey the excitement of the chemical sciences. There are three basic types of students who might take chemistry in an undergraduate setting: One is the chemistry major, one is a science major, and one is a nonscience student. Only about 10 percent or fewer students in the first-year chemistry class will go on to become professional chemists or chemical engineers.<sup>4</sup> Clearly introductory courses must include certain material to build the foundation for advanced work, but this does not mean that the wonder and excitement of chemistry cannot be emphasized. Basic science curricula needs to be developed for non-science undergraduate students. Chemists and chemical engineers should take the lead in collaborating with their scientific colleagues to develop a comprehensive science and technology course to enhance the understanding by non-scientists of the scientific method and the wonder and value of science. It is necessary for scientists and engineers to define the minimum amount of science an educated person with a bachelor's degree in any field should have.

In both chemistry and chemical engineering, greater opportunity and encouragement needs to be given for undergraduates to have a research experience. This needs to be offered through the universities, through programs such as Research Experiences for Undergraduates, through cooperative education programs and summer opportunities at government laboratories.

Chemical scientists must communicate more effectively with other sectors of society, technical and nontechnical alike, beyond the chemical science community. They must put their discoveries and their goals into words that make sense to nonchemists. It cannot be assumed that everyone will recognize that "aromatic" might not refer to odor or that a "reaction" might be something other than the response to a surprise. Chemists and chemical engineers must describe to the media what is important in chemistry. We should recognize the journalist's need for news that the public can understand and the opportunity that this represents to transmit important contributions of the chemical sciences. Perhaps most important, chemical scientists must communicate more effectively with their elected representatives and other government officials. The unified field of chemistry

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<sup>3</sup>*Graduate Education in the Chemical Sciences: Issues for the 21st Century*, National Research Council, National Academy Press, Washington, D.C., 2000.

<sup>4</sup>*Chemical & Engineering News*, 79 (31), 5, 2001

TABLE 12-1 Full-time Graduate Students in Chemistry and Chemical Engineering.<sup>a</sup>

Field	1993	2000
Chemistry	17,204	15,707
Chemical Engineering	6,079	5,865

<sup>a</sup>Data from *Federal Investment in R&D*, E. Eiseman, K. Koizumi, and D. Fossum, RAND Science and Technology Policy Institute, Arlington, VA, 2002 (Table 17), p. 99.

and chemical engineering has an exciting story to tell, with intellectual excitement and practical applications that are critical to modern civilization. The story must be told to those whose decisions affect the resources needed to solve the challenges that are outlined in this report. These goals in the realm of communication constitute a serious challenge to chemical scientists and engineers—to accept an enhanced commitment to professional responsibility and involvement that would provide enormous benefit to their field.

Chemists and chemical engineers can broaden their perceptions and interactions; one goal of this joint report is to facilitate movement in this direction. Name changes in both chemistry and chemical engineering departments have reflected this progression in recent years. Chemical scientists can work to mutual benefit with experts from many other areas—electrical engineers, pharmacologists, materials scientists, and solid-state physicists to name just a few.

The pool of chemists and engineers must be expanded by attracting more women and minorities<sup>5</sup> to the fields that chemical scientists find so rewarding and exciting, as we discuss further in the next section. We must examine our current practices and beliefs to see how to fully tap the talents of all members of our society. U.S. chemistry and chemical engineering benefit from the immigration of individuals with the needed skills who have been trained both here and in other countries. However, the challenges are so great, and the demand for talent so large, that it is important to attract more of the brightest American students into these fields. Despite the needs of our technological society for chemists and chemical engineers (see below), graduate school enrollments in the United States have declined a bit over the last decade (Table 12-1).

Chemists and chemical engineers will need to be active ambassadors for their fields by recruiting new students and describing the satisfaction and rewards of a life on the frontier—in this case the molecular frontier. This will require visits to schools to talk about the careers and opportunities. It is critical that such

<sup>5</sup>For background information on these chemical workforce issues see: *Women in the Chemical Workforce*, National Research Council, National Academy Press, Washington, D.C., 2000; *Minorities in the Chemical Workforce: Diversity Models that Work*, National Research Council, The National Academies Press, Washington, D.C., 2003.

visits include students in the entire range from kindergarten through high school. Students need to learn early that there are exciting things to do in creative science, including in particular the chemical sciences, and that they could play a role in inventing solutions to the challenges that humanity faces. Many students have never met a chemist or chemical engineer, and it may be essential to see that they do.

Finally, chemists and chemical engineers must accept the important challenges that they alone can meet. Some of the challenges are described in this report, but the chemical sciences community must continuously expand the list—and always stand ready to accept new ideas and meet new goals. Some of the most exciting advances in science have come from basic scientific exploration, so we must continue to encourage those who simply want to expand the frontiers of fundamental understanding.

### EDUCATORS

As mentioned above, it is important to convey the excitement of the chemical sciences to students. Science is about discovery, but chemistry and chemical engineering also extend to invention. Showing students how data can be used to make a scientific deduction gives more of a flavor of the science than does simply learning a set of facts about the science. For example, students can gain real contact with primary scientific data and its interpretation if they are asked to look at an NMR spectrum of a compound and deduce its structure. Asking them to invent an experiment that will answer a chemical question can also be stimulating. Asking them how they could synthesize a given compound makes them use their knowledge in a creative way. Some of this can be done in standard lecture and laboratory courses, but it is also important to encourage creativity by promoting science fairs in which high school students can compete by entering their own research projects.

Educators should take advantage of the availability of professional chemists and chemical engineers, who can speak to the students either in class or in some special forum. Contact with practicing scientists can help students put a human face on a possible future career. It is especially important that women and minority scientists also play a role in such outreach to students, to show that indeed the profession welcomes all with the talent to contribute. Some of this effort should be directed toward the early parts of K-12 education. The future of the chemical sciences may depend on the ability of educators to convince young students that “it’s cool to be excited by chemistry.”

### THE MEDIA

Chemistry is to a large extent invisible in newspapers, news magazines, television, and radio. If the message from chemists and chemical engineers is so

exciting, why is it not a focus of media attention? Part of the reason is the tendency of chemical scientists to present their work in such a complex and technical way that it does not translate readily to a general format. Some argue that chemical results are too complicated to present to the public—but that does not seem to inhibit those working in physics, biology, and astronomy, where news coverage of new discoveries seems much more common. Consequently, the challenge is clear. Chemists and chemical engineers must become more proficient in their communication skills—particularly in their interactions with the journalists who will write the final stories. The goals and achievements of chemistry and chemical engineering—in basic science and in meeting human needs—provide ample justification for efforts to work with the media.

As described in this report, the role of chemistry and chemical engineering in modern society is both important and central. It is therefore essential that this message be made clear to the public, to decision makers, and to opinion leaders. As an example, when a new medicine or electronics breakthrough is announced, credit is usually given to those who carried out the last steps—the physicians who tested the drug that was invented by chemists, or the electronics experts who assembled the chemical science and engineering advances into the final version of a chip. As a result, the chemical scientists with responsibility for the original invention may not receive any credit whatsoever, and the public may not recognize that chemists and chemical engineers made essential contributions. Chemical scientists and their professional organizations will need to work with media experts if such patterns are to be changed.

### THE GENERAL PUBLIC

If chemical scientists are to be successful in their efforts to improve the educational experience of their students, they will need help from the public. One step is to assure that there is a general understanding of the ways that chemistry is central to understanding life itself, and to providing the medicines, products, modern materials, and processes that support human needs. But the necessary second step is to enlist the public's support—to have them approve of students' desires to enter the chemical sciences and contribute to its goals and challenges. If parents encourage their sons and daughters to take up such careers, and if the public encourages financial support for research and education in chemistry and chemical engineering, then progress can be expected.

In a recent poll of the general public conducted by the American Chemical Society,<sup>6</sup> chemistry as a career option was ranked third in a list of eight scientific professions, and chemists scored high as visionary, innovative, and results-oriented. Also, 59% said that chemicals made their lives better. These results sug-

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<sup>6</sup>*Chemical & Engineering News*, 78, 41, 60-61, 2000.

TABLE 12-2 Doctoral Scientists and Engineers Employed in the United States in 1999.<sup>a</sup>

Field	Subfield	Number Employed	
Physical Sciences			110,300
	Chemistry	55,810	
Engineering			95,890
	Chemical Engineering	12,520	
Total		68,330	206,190

<sup>a</sup>Data from *Federal Investment in R&D*, E. Eiseman, K. Koizumi, and D. Fossum, RAND Science and Technology Policy Institute, Arlington, VA, 2002 (Table 23), p. 107.

gest that the public would indeed endorse the goals suggested here for enhancing the infrastructure for education and research in the chemical sciences.

### GOVERNMENT AND PRIVATE FOUNDATIONS

Research and education go hand in hand in chemistry and chemical engineering. While it is possible to teach students about the chemistry of the past by lectures alone, participation in research gives them a chance to learn what science really is, and to engage their creative and critical imaginations. In this way, the support of research directly contributes to the education of chemical scientists. It can also provide those students who want to go into other fields—law, business, government—with a real understanding of the basic and applied work in chemistry and chemical engineering.

The unemployment rate for chemists has remained low during the past few years,<sup>7</sup> reaching only the normal rate (2%) for people who are moving from one job to another. Of course, this low unemployment rate can and does rise to some extent in periods when the economy is weak, but chemistry and chemical engineering have a huge advantage over many other disciplines. There is a very large industry that uses chemistry to produce its products, so the opportunities for those who are chemically trained include industrial jobs—not just the academic jobs that some other disciplines have as their only option. Indeed, about two-thirds of the members of the American Chemical Society work in chemically related industries. The Bureau of Labor Statistics reports that in 2000, employment in the United States included more than 92,000 chemists and materials scientists, 73,000 chemical technicians, and 33,000 chemical engineers.<sup>8</sup> Table 12-2 shows that

<sup>7</sup>*Chemical & Engineering News*, 79, 46, 38-39, 2001.

<sup>8</sup>U.S. Department of Labor, Bureau of Labor Statistics: Occupational Outlook Handbook, 2002-03 Edition, <http://www.bls.gov/oco/home.htm>.

chemists comprised just over fifty percent of the doctoral level physical scientists in the U.S. workforce in 1999, while chemists and chemical engineers together made up approximately one-third of all the doctoral-level physical scientists and engineers.

The basic research in our fields is now done largely in universities. It can have incredibly important practical results, but those results cannot normally be predicted in advance. Who would have thought that the basic study of induced energy emission from excited states of atoms and molecules that led to the laser would wind up giving us a better way to record music, or read supermarket prices? Would a music company have funded that research? Who would have thought that our increased understanding of the chemistry of life would have led to the creation of biotechnology as an entirely new industry? The industry that benefited from the basic research could not have funded it, since it did not yet exist.

U.S. companies swiftly use the new leads from basic research in U.S. universities, in part because they have good contacts, and in part because they hire students or even faculty who have played a role in creating that basic knowledge. However, support of the research itself is mainly the function of the federal government, and to a lesser extent of private foundations. A recent study carried out by the Council for Chemical Research finds that on average, every \$1 invested in chemical R&D today produces \$2 in corporate operating income over six years—an average annual return of 17% after taxes.<sup>9</sup> The study also reports a strong linkage of industrial patents to publicly funded academic research.

Federal agencies have been the major supporters of research and education in the chemical sciences. For example, the National Institutes of Health (NIH) provide very important support to health-related science in universities, including health-related chemistry and chemical engineering. This support has been directed to basic science as well as to more applied studies. Thus NIH has supported the basic work to understand the chemistry of proteins and of nucleic acids, fundamental building blocks of living systems. To assure continued support by the NIH, it is important that the health relevance of chemistry and chemical engineering be clearly and explicitly recognized. After all, chemistry underlies the understanding of the basic processes of life, as was described in Chapter 7. Also, the pharmaceutical industry, agriculture, and sanitation are the three principal contributors to human health, and all three are heavily based on chemistry. Chemists and chemical engineers constitute a large fraction of the scientists doing research in pharmaceutical companies, inventing the medicines and the processes for manufacturing them. Their education and training in U.S. universities is possible only with adequate support by the NIH, support with both research grants and training grants.

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<sup>9</sup>*Measuring Up: Research & Development Counts in the Chemical Industry*, Council for Chemical Research, Washington, D.C., 2000; <http://www.ccrhq.org/news/studyindex.html>.

TABLE 12-3 Federal Funding for Research in Science and Engineering  
(Millions of 2000 Dollars)<sup>a</sup>

Field	1970	1975	1980	1985	1990	1995	2000
Total, all S&E	18,104	18,606	22,141	23,467	26,860	31,005	38,471
Physical sciences, total	3,496	3,032	3,819	4,431	4,731	4,665	4,788
Chemistry	841	790	868	946	946	942	1,226
Engineering, total	5,687	4,749	5,403	5,262	5,250	6,224	6,346
Chemical Engineering	404	232	184	370	301	268	197

<sup>a</sup>Data from *Federal Investment in R&D*, E. Eiseman, K. Koizumi, and D. Fossum, RAND Science and Technology Policy Institute, Arlington, VA, 2002 (Table 13), p. 89.

The National Science Foundation (NSF) provides support to all the basic sciences and engineering in universities. NSF support of chemistry is very important, both the support directed to fundamental research initiated by individual investigators and the research done in research centers such as those aimed at developing new materials or at understanding and improving the environment. The support is critical, but more is needed for the chemistry division of NSF to achieve its objectives.<sup>10</sup> Considering the importance of basic and applied chemistry and chemical engineering to the economic future of the United States, it seems that an increase in the ability of NSF to support fundamental and applied chemical science is warranted.

The Department of Energy (DOE), the Department of Defense (DOD), the Environmental Protection Agency (EPA), all help support fundamental and applied chemistry and chemical engineering. Their support is fully justified, as previous sections of this report make clear. The Department of Agriculture (DOA) also has a program of external support for chemistry and chemical engineering in universities, in line with the role that chemistry and chemical engineering play in agriculture.

Table 12-3 summarizes federal funding for research in the physical sciences and engineering over the last several decades. The numbers are reported in constant dollars to facilitate comparisons across different years while minimizing the effects of inflation. While there has been an overall steady increase in federal support since 1970, the support for chemistry has lagged considerably behind the overall trend, and the support for chemical engineering has actually decreased. Strong support for chemistry and chemical engineering in the future will be essential for scientific and technical progress—both to facilitate new discoveries and to provide the technical workforce that will be needed to sustain the U.S. economy.

<sup>10</sup>*Chemical & Engineering News*, 80, 42, 37-39, 2002.

There is another way that federal government officials could provide support for the conclusions of this report—endorse the importance of the challenges and goals that it describes. The federal government has a clear stake in supporting enhanced education and training of chemical scientists and in encouraging recruitment of more U.S. students to these fields. The major role of the chemical industry emphasizes how the economic future of the United States depends on continued scientific excellence in chemistry and chemical engineering.

Many private foundations have agendas that are somewhat narrowly focused—for example, on a disease such as cancer. They often recognize the role that chemical scientists play in understanding the basic biology of the disease and in inventing medicines for treatment or procedures for delivering such medicines. Although their funding cannot replace federal support, the special programs they create are valuable as support for research and education. Other foundations provide extremely valuable support for young chemical scientists at the early stages of their careers—when their records of accomplishment may not yet be adequate to let them compete successfully for federal funding.

## INDUSTRY

The chemical industry is involved with all parts of the chemical sciences. U.S. companies hire university graduates, carry out R&D programs, engage in joint efforts with universities and national laboratories, and generate ideas that stimulate further research in the academic arena. Consequently, it is of central importance to the chemical industry that the health of chemistry and chemical engineering be maintained. There are many ways that U.S. companies can help. One is to continue the demonstrated progress in environmentally benign manufacturing as exemplified by the Responsible Care program. Past practices that led to well-publicized problems are now recognized, changes have been implemented, and improvements continue to be made. The more chemistry-based industry can improve its public reputation, the better the consequences for chemists and chemical engineers.

When a new medicine is announced, it is important that companies publicly recognize the chemistry that went into its creation and the chemical engineering that went into the manufacturing process. When other valuable new products are introduced, companies should not be afraid to describe the contribution of chemical scientists. The negative public reactions from past problems with chemical manufacturing have led some companies to nearly hide the fact that they do chemistry. But if chemical companies can discuss behavior of which they are proud, they may be willing to assert that they indeed do chemistry, and do it well. Pretending otherwise demeans the entire profession and the incredible contributions that it makes.

There is a serious problem with public perception that the chemical industry needs to correct. In a survey of 1,012 U.S. adults commissioned by the American

Chemical Society (see above) only 43% had a favorable opinion of the chemical industry. It was ranked lowest among a list of 10 industries, and only 1 in 10 respondents felt very well informed about the role of chemicals in improving human health. The situation is not appreciably better elsewhere. In Canada only 40% of adults in a 1999 survey had a favorable view of the chemical industry, and only 18% felt that the industry was excellent or good at being honest. A survey of 9,000 Western European citizens by the European Chemical Industry Council showed that only 45% had a favorable view of the chemical industry. There is still a lot of work to do to change these opinions and perceptions.

Chemistry departments and chemical engineering departments in universities need more help from industry. After all, companies need both the research advances and the trained people that universities produce. At one time these companies provided significant support, for example in the form of fellowships for Ph.D. students. As research support shifted to the federal government in the second half of the 20th century, many of these industrial programs disappeared. They are now needed again, especially in the form of graduate fellowships, as some of the federal fellowship programs have been terminated.

As industrial R&D moves forward in an increasingly interdisciplinary fashion, it will be important for the chemical industry to recognize this trend in its hiring procedures. If interdisciplinary and multidisciplinary work is to be encouraged, industry will need to seek and hire people who have worked at the intersections of chemistry and chemical engineering with biology, physics, and other sciences.

## GRAND CHALLENGES

This report has summarized the contributions that chemical science and engineering have already made to human welfare and to economic strength. It has focused to some extent on these contributions to the United States, but in truth all of humanity benefits from advances in medicines, in a better environment, in energy production and distribution, in materials production, information science, and national security. On the one hand, this report draws attention to the rich intellectual challenge of understanding our world through the chemical sciences. On the other hand, it points out the very close connection between basic research and useful applications in the chemical sciences. Basic science creates opportunities for exciting practical advances, but work to solve practical problems often stimulates enquiry into new areas of basic science. Thus, the connections among all aspects of chemistry and chemical engineering are strong and important.

There is still much to be done. In every chapter of this report some of the remaining challenges for the field are described, together with the importance of meeting those challenges. In addition, some especially exciting challenges start each chapter. Chemistry and chemical engineering are very diverse fields, which do not focus on only one or two central problems. This is in part their strength,

since it means that they can make contributions to wide areas of human understanding and human welfare. At the same time, it is a problem because great advances can be made in one area without necessarily revolutionizing the entire field. Some of the challenges are specific, but others are quite broad, with potential impact well beyond the chemical sciences. These are listed here as some overriding themes, described as *grand challenges*—they are broad opportunities that if met could have huge benefits to society. While they are goals not yet reached, we propose that they can be realistically addressed with the new and developing strengths in theories and procedures in the chemical sciences. As we continue to push forward the frontiers of science, we will increasingly do so by working with our colleagues in other disciplines. In this way, the chemical sciences will be able to contribute in remarkable ways to an improved future for our country, for humanity, and for our planet.

We caution the reader that these grand challenges should not be taken as the only areas for worthwhile research. The history of science shows again and again that large revolutions in thought can arise from discoveries that were made by individuals or teams who were not constrained by someone else's list. Chemistry and chemical engineering enter the 21st century with exciting science ahead and major contributions to make. The committee hopes this report will stimulate young people to join them in meeting these challenges, and that society will support continued efforts of chemists and chemical engineers in their work on and beyond the molecular frontier.

### Some Grand Challenges for Chemists and Chemical Engineers

- **Learn how to synthesize and manufacture any new substance that can have scientific or practical interest, using compact synthetic schemes and processes with high selectivity for the desired product, and with low energy consumption and benign environmental effects in the process.** This goal will require continuing progress in the development of new methods for synthesis and manufacturing. Human welfare will continue to benefit from new substances, including medicines and specialized materials.
- **Develop new materials and measurement devices that will protect citizens against terrorism, accident, crime, and disease, in part by detecting and identifying dangerous substances and organisms using methods with high sensitivity and selectivity.** Rapid and reliable detection of dangerous disease organisms, highly toxic chemicals, and concealed explosives (including those in land

*continues*

mines), is the first important step in responding to threats. The next important step for chemists and chemical engineers will be to devise methods to deal with such threats, including those involved in terrorist or military attacks.

- **Understand and control how molecules react—over all time scales and the full range of molecular size.** This fundamental understanding will let us design new reactions and manufacturing processes and will provide fundamental insights into the science of chemistry. Major advances that will contribute to this goal over the next decades include: the predictive computational modeling of molecular motions using large-scale parallel processing arrays; the ability to investigate and manipulate individual molecules, not just collections of molecules; and the generation of ultrafast electron pulses and optical pulses down to x-ray wavelengths, to observe molecular structures during chemical reactions. This is but one area in which increased understanding will lead to a greater ability to improve the practical applications of the chemical sciences.
- **Learn how to design and produce new substances, materials, and molecular devices with properties that can be predicted, tailored, and tuned before production.** This ability would greatly streamline the search for new useful substances, avoiding considerable trial and error. Recent and projected advances in chemical theory and computation should make this possible.
- **Understand the chemistry of living systems in detail.** Understand how various different proteins and nucleic acids and small biological molecules assemble into chemically defined functional complexes, and indeed understand all the complex chemical interactions among the various components of living cells. Explaining the processes of life in chemical terms is one of the great challenges continuing into the future, and the chemistry behind thought and memory is an especially exciting challenge. This is an area in which great progress has been made, as biology increasingly becomes a chemical science (and chemistry increasingly becomes a life science).
- **Develop medicines and therapies that can cure currently untreatable diseases.** In spite of the great progress that has been made in the invention of new medicines by chemists, and new materials and delivery vehicles by engineers, the challenges in these directions are vast. New medicines to deal with cancer, viral diseases, and many other maladies will enormously improve human welfare.
- **Develop self-assembly as a useful approach to the synthesis and manufacturing of complex systems and materials.** Mixtures of

properly designed chemical components can organize themselves into complex assemblies with structures from the nanoscale to the macroscale, in a fashion similar to biological assembly. Taking this methodology from the laboratory experimentation to the practical manufacturing arena could revolutionize chemical processing.

- **Understand the complex chemistry of the earth, including land, sea, atmosphere, and biosphere, so we can maintain its livability.** This is a fundamental challenge to the natural science of our field, and it is key to helping design policies that will prevent environmental degradation. In addition, chemical scientists will use this understanding to create new methods to deal with pollution and other threats to our earth.
- **Develop unlimited and inexpensive energy (with new ways of energy generation, storage, and transportation) to pave the way to a truly sustainable future.** Our current ways of generating and using energy consume limited resources and produce environmental problems. There are very exciting prospects for fuel cells to permit an economy based on hydrogen (generated in various ways) rather than fossil fuels, ways to harness the energy of sunlight for our use, and superconductors that will permit efficient energy distribution.
- **Design and develop self-optimizing chemical systems.** Building on the approach that allows optimization of biological systems through evolution, this would let a system produce the optimal new substance, and produce it as a single product rather than as a mixture from which the desired component must be isolated and identified. Self-optimizing systems would allow visionary chemical scientists to use this approach to make new medicines, catalysts, and other important chemical products—in part by combining new approaches to informatics with rapid experimental screening methods.
- **Revolutionize the design of chemical processes to make them safe, compact, flexible, energy efficient, environmentally benign, and conducive to the rapid commercialization of new products.** This points to the major goal of modern chemical engineering, in which many new factors are important for an optimal manufacturing process. Great progress has been made in developing Green Chemistry, but more is needed as we continue to meet human needs with the production of important chemical products using processes that are completely harmless to the earth and its inhabitants.
- **Communicate effectively to the general public the contributions that chemistry and chemical engineering make to society.** Chem-

*continues*

ists and chemical engineers need to learn how to communicate effectively to the general public — both through the media and directly — to explain what chemists and chemical engineers do and to convey the goals and achievements of the chemical sciences in pursuit of a better world.

- **Attract the best and the brightest young students into the chemical sciences, to help meet these challenges.** They can contribute to critical human needs while following exciting careers, working on and beyond the molecular frontier.

# Appendixes



# A

## Biographical Sketches of Steering Committee Members

**Ronald Breslow** (*Co-Chair*) is University Professor of Chemistry, Columbia University, and a founder of a new pharmaceutical company. He received his B.A. (1952), M.A. (1954), and Ph.D. (1955) from Harvard University. His research area is organic chemistry with specialization in biochemical model systems, biomimetic synthetic methods, reaction mechanisms, and aromaticity and antiaromaticity. He served as president of the American Chemical Society in 1996 and has authored a book for the general public, *Chemistry Today and Tomorrow: The Central, Useful, and Creative Science*. He is a member of the National Academy of Sciences, the American Academy of Arts and Sciences, and the American Philosophical Society. He received the U.S. National Medal of Science in 1991.

**Matthew V. Tirrell** (*Co-Chair*) is Dean of the College of Engineering at the University of California at Santa Barbara. He was previously Professor and Head of the Department of Chemical Engineering and Materials Science at the University of Minnesota, where he served as Director of its Biomedical Engineering Institute. He received a B.S. from Northwestern University and a Ph.D. from University of Massachusetts. His interests are in transport and interfacial properties of polymers, with particular emphasis on molecular-scale mechanical measurements, bioadhesion, and new materials development. He is a member of the National Academy of Engineering.

**Jacqueline K. Barton** is Arthur and Marian Hanisch Memorial Professor of Chemistry at the California Institute of Technology. She received her A.B. from Barnard College in 1974 and her Ph.D. from Columbia University in 1979. She did subsequent postdoctoral work at both AT&T Bell Laboratories and Yale Uni-

versity. Her research areas are biophysical chemistry and inorganic chemistry. She has focused on studies of recognition and reaction of nucleic acids by transition metal complexes, and particularly DNA-mediated charge transport chemistry. She is a member of the Board of Directors of the Dow Chemical Company and a member of the National Academy of Sciences.

**Mark A. Barteau** is Robert L. Pigford Professor and Chair of the Department of Chemical Engineering at the University of Delaware. He received his B.S. degree from Washington University in 1976 and his M.S. (1977) and Ph.D. (1981) from Stanford University. His research area is chemical engineering with specialized interests in application of surface techniques to reactions on nonmetals, hydrocarbon and oxygenate chemistry on metals and metal oxides, scanning probe microscopies, and catalysis by metal oxides.

**Carolyn R. Bertozzi** is Professor of Chemistry and Molecular and Cell Biology at the University of California, Berkeley, a Junior Investigator of the Howard Hughes Medical Institute, and Faculty Associate of the Materials Sciences and Physical Biosciences divisions of the Lawrence Berkeley National Laboratory. She received her A.B. from Harvard University in 1988 and her Ph.D. from the University of California, Berkeley, in 1993. Her research focuses on organic chemistry and the combination of molecular and cell biology to investigate the biological functions of glycoconjugates and to develop new therapeutic strategies.

**Robert A. Brown** is Warren K. Lewis Professor of Chemical Engineering and Provost at the Massachusetts Institute of Technology. He received his B.S. (1973) and M.S. (1975) from the University of Texas, Austin, and his Ph.D. from the University of Minnesota in 1979. His research area is chemical engineering with specialization in fluid mechanics and transport phenomena, crystal growth from the melt, microdefect formation in semiconductors and viscoelastic fluids, bifurcation theory applied to transitions in flow problems, and finite element methods for nonlinear transport problems. He is a member of the National Academy of Engineering, the National Academy of Sciences, and the American Academy of Arts and Sciences.

**Alice P. Gast** (*BCST liaison*) is Vice President for Research and Associate Provost at the Massachusetts Institute of Technology, where she coordinates policy regarding research and graduate education and oversees the Institute's large interschool laboratories. In addition to her administrative positions, she is the Robert T. Haslam Professor of Chemical Engineering. Prior to her appointment at MIT, Dr. Gast was Associate Chair and Professor of the Department of Chemical Engineering at Stanford University, having joined the Stanford faculty in 1985. She received her B.Sc. in chemical engineering (1980) from the Univer-

sity of Southern California and her M.A. (1981) and Ph.D. (1984) from Princeton. Her research expertise is in the area of complex fluids and colloids, with a focus on frontiers of the chemical physics of colloidal and polymer solutions, polymer adsorption, and, most recently, proteins, using experimental scattering methods and statistical mechanics. She is a member of the National Academy of Engineering.

**Ignacio E. Grossmann** is Rudolph H. and Florence Dean Professor and head of the chemical engineering department at Carnegie Mellon University. He received his B.Sc. (1974) from Universidad Iberoamericana, Mexico, and his M.Sc. (1975) and Ph.D. (1977) degrees from Imperial College, London. He joined Carnegie Mellon in 1979 and has focused his research on the synthesis of integrated flow sheets, batch processes, and mixed-integer optimization. The goals of his work are to develop novel mathematical programming models and techniques in process systems engineering. He was elected to the Mexican Academy of Engineering in 1999, and he is a member of the National Academy of Engineering.

**James M. Meyer** retired in 2001 as Vice President of DuPont Central Research and Development. He joined DuPont in 1969 and held a variety of research and management positions related to elastomers and polymers. He moved to Central Research and Development in 1992 as director of materials science and engineering, and he assumed his current position in 1996. Dr. Meyer received his B.S. degree in chemistry from Indiana University and his Ph.D. degree in inorganic chemistry from Northwestern University.

**Royce W. Murray** is Kenan Professor of Chemistry at the University of North Carolina at Chapel Hill. He received his B.S. from Birmingham Southern College in 1957 and his Ph.D. from Northwestern University in 1960. His research areas are analytical chemistry and materials science with specialized interests in electrochemical techniques and reactions, chemically derivatized surfaces in electrochemistry and analytical chemistry, electrocatalysis, polymer films and membranes, solid state electrochemistry and transport phenomena, and molecular electronics. He is a member of the National Academy of Sciences.

**Paul J. Reider** is Vice President of Chemistry Research at Amgen, Inc. Before moving to Amgen in 2002, he was Vice President of Process Research at Merck Research Laboratories. His research has focused on synthetic organic and natural product chemistry for the development of pharmaceuticals, and he has worked extensively on drugs for AIDS, asthma, arthritis, and bacterial infections. He received his A.B. from Washington Square College in 1972 and his Ph.D. from the University of Vermont in organic chemistry in 1978. As a National Research Awardee (NIH) he did his postdoctoral work at Colorado State University.

**William R. Roush** is Warner Lambert/Parke Davis Professor of Chemistry at the University of Michigan. He received his B.S. from the University of California, Los Angeles, in 1974 and his Ph.D. from Harvard University in 1977. His research area is organic chemistry, with specialized interests in organic synthesis and natural products chemistry, stereochemistry of organic reactions, development of new methods and reagents, asymmetric synthesis, and oligosaccharide synthesis.

**Michael L. Shuler** is Director and Professor of the School of Chemical Engineering and Director of Bioengineering at Cornell University. He received his B.S. from the University of Notre Dame in 1969 and his Ph.D. from the University of Minnesota in 1973. His research area is chemical engineering with specialized interests in mathematical models of cellular growth, plant cell suspension cultures, utilization of genetically modified cells, insect cell cultures, novel bioreactors, environmental biotechnology, and pharmacokinetic models and cell culture analog systems. He is a member of the National Academy of Engineering.

**Jeffrey J. Siivola** is a Research Fellow in the Chemical Process Research Laboratory at Eastman Chemical Company in Kingsport, TN. He received his B.S. degree in chemical engineering from the University of Utah in 1967 and his Ph.D. in chemical engineering from the University of Wisconsin-Madison in 1970. His research centers on chemical processing, including chemical process synthesis, computer-aided conceptual process engineering, engineering design theory and methodology, chemical technology, assessment, resource conservation and recovery, artificial intelligence, nonnumeric (symbolic) computer programming, and chemical engineering education. He is a member of the National Academy of Engineering.

**George M. Whitesides** is Mallinckrodt Professor of Chemistry at Harvard University. He received his A.B. from Harvard College in 1960 and his Ph.D. from the California Institute of Technology in 1964. His research areas are Materials Science and Organic Chemistry, with specific focus in surface chemistry, materials science, self-assembly, capillary electrophoresis, organic solid state, molecular virology, directed ligand discovery, and protein chemistry. He is a member of the National Academy of Sciences, and he received the U.S. National Medal of Science in 1998.

**Peter G. Wolynes** is Professor of Chemistry and Biochemistry at the University of California, San Diego. He was previously Professor of Chemistry at the University of Illinois at Urbana-Champaign. He received his A.B. from Indiana University in 1971 and his Ph.D. from Harvard University in 1976. His research area is physical chemistry with specialized interests in chemical physics of condensed matter, quantum dynamics and reaction kinetics in liquids, dynamics of complex

fluids, phase transitions and the glassy state, and biophysical applications of statistical mechanics, especially protein folding. He is a member of the National Academy of Sciences.

**Richard N. Zare** is Marguerite Blake Wilbur Professor in Natural Science in the Department of Chemistry at Stanford University. He received his B.A. in 1961 and his Ph.D. in 1964 from Harvard University. His research areas are physical and analytical chemistry with specialized interests in application of lasers to chemical problems, molecular structure, molecular reaction dynamics, and chemical analysis. Zare has been a member of various NRC committees and served as co-chair of the Commission on Physical Sciences, Mathematics, and Applications and chair of the National Science Board. He is a member of the National Academy of Sciences, and he received the U.S. National Medal of Science in 1983.

# B

## Statement of Task

The overview report will identify recent advances and current challenges in fundamental understanding of the basic science, and it will explore the impact beyond the chemical sciences that these advances have had in the past. It will also explore the possibilities for such impact in the future, recognizing that such developments are frequently serendipitous. Issues to be addressed include:

- **Discovery:** Identify major discoveries or advances in the chemical sciences during the last several decades, and evaluate their impact—including the length of time for impact beyond basic chemical sciences to be realized.
- **Interfaces:** Identify the major discoveries and challenges at the interfaces between chemistry/chemical engineering and such areas as biology, environmental science, materials science, medicine, and physics.
- **Challenges:** Identify the grand challenges that exist in the chemical sciences today. Explore how advances at the interfaces create new challenges in the core disciplines.
- **Infrastructure:** Identify infrastructure that will be required to allow the potential of future advances in the chemical sciences to be realized. Identify opportunities that exist to integrate research and teaching, broaden the participation of underrepresented groups, improve the infrastructure for research and education, and demonstrate the value of these activities to society.

# C

## Contributors

When the Challenges for the Chemical Sciences in the 21st Century project was initiated in 2000, the Committee solicited input from the chemical sciences community. A specific request for input was sent via e-mail to a large number of scientists and engineers, and a general request for information appeared in *Chemical & Engineering News*.<sup>1</sup> In addition to the responses to these requests, input from the broader community was obtained as the committee wrote this report, when individual members of the committee consulted with their colleagues to obtain specific and detailed technical input. The committee is pleased to acknowledge the assistance of all these contributors:

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<sup>1</sup>“Your Ideas, Please!” Madeleine Jacobs, Editor-in-chief, *Chemical & Engineering News*, 78(14), April 3, 2000.

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