Putting Biotechnology to Work

Bioprocess Engineering

National Research Council

PUTTING BIOTECHNOLOGY TO WORK

BIOPROCESS ENGINEERING

Committee on Bioprocess Engineering

Board on Biology

Commission on Life Sciences

National Research Council

NATIONAL ACADEMY OF SCIENCES
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Preface

Biotechnology is broadly defined in a 1991 Office of Technology Assessment report as "any technique that uses living organisms (or parts of organisms) to make or modify products, to improve plants or animals, or to develop microorganisms for specific uses." This technology has been instrumental in the development and implementation of processes for the manufacture of antibiotics and other pharmaceuticals, industrial sugars, alcohols, amino acids and other organic acids, foods, and specialty products through the application of microbiology, fermentation, enzymes, and separation technology. Engineers, working with life scientists, often achieved scale-up to industrial production in remarkably short periods. A relatively small number helped to catalyze, over a period of 50 years, the growth of the pharmaceutical, food, agricultural-processing, and specialty-product sectors of the U.S. economy to the point where sales now exceed $100 billion/year.

The introduction of the new biotechnology since 1970 enabled directed manipulation of the cell's genetic machinery through recombinant-DNA techniques and cell fusion. Its application on an industrial scale since 1979 has fundamentally expanded the utility of biological systems and positioned a number of industries for explosive global growth. Scientists and engineers can now change the genetic makeup of microbial, plant, and animal cells to confer new characteristics. Biological molecules, for which there is no other means of industrial production, can now be generated. Existing industrial organisms can be systematically altered (i.e., engineered) to enhance their function and to produce useful products in new ways. The new biotechnology, combined with the existing industrial, government, and university infrastructure in biotechnology and the pervasive influence of biological substances in everyday life, has set the stage for unprecedented growth in products, markets, and expectations.

Substantial manufacturing capability will be needed to bring about the full application of biotechnology for the benefit of society. A wide array of engineering fundamentals applied to biological systems will be required to produce and purify biological products on a commercial scale. Bioprocess engineers will be essential for translating the discoveries of biotechnology into tangible commercial products, thereby putting biotechnology to work. The Committee on Bioprocess Engineering was convened in the National Research Council's Board on Biology to address issues that are of critical importance if the nation is to reap the full benefits of its success in fundamental biotechnology research: What discoveries and concepts in biology and chemistry are important to bioprocess engineering? What barriers to their exploitation exist? What is the position of the United States in relation to other countries' efforts in bioprocess engineering, especially those of Japan and Germany? What actions are required to ensure that research and training are adequately organized and supported so that the United States can maintain and improve its position? The committee met five times from May 1991 to May 1992 and found that much needs to be done, and done quickly. This report represents a consensus of the committee, which hopes to impart a sense of urgency to the planning for bioprocess-engineering needs in biotechnology manufacturing in the United States.

The committee carefully considered the best way to present its findings and to organize the report, given the wide range of products, services, and needs that will be affected by bioprocess engineering and the diverse backgrounds of those who will read this report. The committee decided that the reader should first be provided a definition of bioprocess engineering, a discussion of its economic impact on biotechnology, and a summary of major barriers to the exploitation of biotechnology. Further definitions and a historical perspective were to be addressed in Chapter 2, to illustrate the role of bioprocess engineering in a substantial portion of the economic sectors of the United States. We decided to present the current status of U.S. capabilities, and those of Japan and Europe next, because of the importance of international competitiveness for U.S. economic activities, particularly those affected by bioprocessing. The many areas already affected by bioprocess engineering are presented in Chapter 4, to help the reader become more aware of the language and technologies encompassed by biotechnology. Having "set the stage," the committee chose to present, in Chapter 5, what needs to be done now to address needs that will not be fully understood for some years to come. Chapter 6 addresses future scenarios of biotechnology development and how the education, training, research, and technology-transfer issues related to current opportunities (described in Chapter 5) will prepare bioprocessing to address future needs.

The committee thanks those who contributed to its work and shared their expertise at our meetings. In particular, we would like to thank the National Science Foundation (NSF) Directorate for Engineering (Biotechnology Program and Divisions of Biological and Critical Systems, Engineering Education Centers, and Chemical and Thermal Systems), the NSF Directorate for Biological Sciences (Divisions of Behavioral and Cognitive Sciences, Biological Instrumentation and Resources, Social and Economic Science, and Molecular Biosciences), the Department of Energy (offices of Industrial Technologies, Fossil Energy, and Alcohol Fuels), the Department of Agriculture (Office of the Assistant Secretary for Science and Education and Agricultural Research Service), the National Aeronautics and Space Administration (Life Sciences Division, Microgravity Science Division, and Office of Commercial Programs), the Department of Commerce (National Institute of Standards and Technology, Chemical Science and Technology Laboratory), and the National Academy of Engineering for funding this study. Duane Bruley, Luther Williams, and Carl Hall of NSF deserve special mention for their support of this study in its early stages and Fred Heineken of NSF for serving as the contact person of the lead agency on logistic matters.

The chairman thanks Purdue University for making time available to carry out the tasks associated with the committee's work, Carolyn Wasson for excellent assistance in preparing the various drafts of this report, and Norma Leuck for coordinating the numerous communications with committee members. The chairman also thanks Michael Shuler of Cornell University for making his expertise available and contributing to the technical completeness of the report; Charles Scott of Oak Ridge National Laboratories for comments on bioprocess-engineering needs; Edith Munroe of the Corn Refiners Association, Inc., and Matthew Rendlemen and Betsy Kuhn of the Department of Agriculture Economic Research Service for helpful information on value-added products from corn; and Karl H. Kroner of the German National Research Center for Biotechnology (GBF) for providing information on German bioprocess engineering. The committee thanks Donald Henninger, Doug Ming, and Glenn Spaulding of the National Aeronautics and Space Administration Johnson Space Center for arranging a subcommittee visit to the center and is indebted to Marietta Toal of the Board on Biology for her excellent assistance with committee meetings. The committee also thanks numerous individuals and organizations that rapidly responded to inquiries from the committee. Norman Grossblatt, of the National Research Council's Commission on Life Sciences, edited the report. Special thanks are due to Oskar Zaborsky, director of the Board on Biology, whose vision, hard work, and many capabilities enabled this study to be initiated and carried out in a timely manner, and to him and John Burris, executive director of the Commission on Life Sciences, for the long hours they spent in guiding this report through many drafts to its successful conclusion.

Michael R. Ladisch, Chairman
Committee on Bioprocess Engineering

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Executive Summary

The United States has dominated the discovery phase of biology and laid the groundwork for commercialization of biotechnology. Biotechnology-derived products already affect human health, nutrition, and environmental improvement and will grow to provide new products and employment in new industries. Worldwide markets for biotechnology-derived products are projected to grow to at least $50 billion per year within the next 10 years, and our global trading partners are concentrating their resources on translating the discoveries of biology into economically viable products through bioprocess engineering.

Bioprocess engineering is the subdiscipline within biotechnology that is responsible for translating life-science discoveries into practical products, processes, or systems capable of serving the needs of society. It is critical in moving newly discovered bioproducts into the hands of the consuming public. Although the United States has nurtured the discovery phase of biotechnology, it has not been aggressive in developing bioprocess engineering.

BIOPROCESS ENGINEERING AND GLOBAL COMPETITIVENESS

The importance of engineering capability in achieving and maintaining global competitiveness is compelling; witness the growth of the pharmaceutical industry after the development of penicillin production during World War II and of the computer and electronics industry after the discovery of the transistor. The strength of the United States in engineering and manufacturing technology made major contributions to America's early dominance of world markets in both instances.

The U.S. ambivalence toward bioprocess engineering is an inadvertent consequence of the high biochemical potency of the protein-based pharmaceuticals introduced between 1982 and 1989 whose worldwide markets are measured in kilograms per year and whose sales are in billions of dollars. But the situation is changing. The emerging families of food, agricultural products, and industrial chemicals to be generated by biological routes, as well as the biopharmaceutical products now in development, will have markets measured in thousands of kilograms, or more, and will require innovative manufacturing techniques.

The participation of the United States in the expanding bioproducts markets will necessitate world-class bioprocess engineering. Comparison of the global competitive position of the United States with that of other technologically advanced nations in biotechnology and bioprocess engineering reveals that

- The United States continues to be the world leader in basic health-science and life-science elements of biotechnology.
- Japan leads in applied microbiology and biocatalysis and is effectively coordinating government, industrial, and academic resources in biotechnology and bioprocess-engineering development.
- Europe matches Japan in progress in applied biocatalysis and is establishing a strong, government-supported technology-transfer infrastructure between industry and academe with emphasis on bioprocess engineering.

World competition in biotechnology and other industries that depend on bioprocess engineering will be keen because of the notable capabilities in and commitments to biologically relevant manufacturing and bioprocess development among industrially developed nations. It is debatable whether the United States can be dominant (or even competitive) in bioprocessing: university research and training programs are projected to grow by 75% in the best case while the industry grows by 1,000% in the next 10 years. The committee concurs with the Federal Coordinating Council on Science, Engineering, and Technology assessment that "manufacturing/bioprocessing is an area in which biotechnology offers vast potential rewards. The total federal investment of $99 million in FY 1992 is small in proportion to its potential."

The committee recommends that the U.S. government promptly take action and provide suitable incentives to establish a national program in bioprocess-engineering research, development, education, and technology transfer. That will require that the existing resources of government, industry, and academe collaborate in

- Rapidly translating scientific discoveries into marketable products and processes.

• Promoting cross-disciplinary research and education and thereby fostering innovative, multidisciplinary solutions to important bioprocessing problems.
• Providing a growing cadre of bioprocess engineers to meet the needs of an expanding bioprocess industry.

OPPORTUNITIES

The committee addressed trends in biotechnology that are likely to have important worldwide social and financial impact within the next 10 years. In this context, current commercial activities related to biotechnology and biotechnology products are dominated by biopharmaceutical biologics, such as insulin, tissue plasminogen activator, and erythropoietin. Innovative bioprocess engineering in the manufacture of these products can lead to improvements in product recovery, product purity, process safety, and reduced manufacturing and quality-control costs. The need for such process innovation will intensify as patent protection for these products expires, global competition for international markets increases, and regulatory procedures that would otherwise slow introduction of new bioprocess technologies are streamlined. Health-care products emerging from biotechnology will be consumed in much larger quantities around the world than they are now (examples include recombinant hemoglobin, recombinant albumin, and conjugate vaccines). These second-generation products will require large-scale manufacturing facilities that handle biological systems; and bioprocess engineering will be a *sine qua non* for successful commercialization of the products.

Bioprocess engineers will be employed in applying the new biology to producing smaller molecules and specialty bioproducts. These are in a category where the challenge is to apply bioprocessing to obtain value-added products and to engineer large-scale, integrated processes that use agricultural and forestry-based materials and other renewable resources. Bioproducts for use in food production and in foods (animal health-care biologics, biological plant-growth promoters and pesticides, nutritional supplements, and food additives) present large-tonnage product opportunities that can be tapped in the coming decade, provided that suitably efficient and economical manufacturing facilities can be designed and built. Such capabilities do not exist, and their creation is a major challenge for bioprocess engineering. The use of biomass for the production of industrial chemicals and of liquid and gaseous fuels represents a major hope for reducing U.S. dependence on imported hydrocarbons. The processing of renewable resources must have high national priority in the coming decade, so that the necessary know-how and production infrastructure for its practical implementation can be developed. Bioprocessing in space presents unique opportunities, particularly in bioregenerative life support and as a research platform for the study of new types of manufacturing processes.

Bioprocessing for protection and beneficiation of the environment represents another large and important opportunity. Biological processes could offer alternatives to environmentally polluting or fossil-fuel-consuming manufacturing processes and could help to remove toxic pollutants from industrial and municipal wastes. Bioremediation's promise is in its potentially lower cost, compared with other types of technology for cleaning up the environment.

NEEDS

Generic applied research is critical to the optimal exploitation of bioprocess engineering by industry, in that it addresses technologies that are too risky for companies or that require too long a period for results. This category of research bridges the gap between basic biological science that is carried out by university and government laboratories and the industrial applied research that assists in converting biotechnology into products and services. For biopharmaceuticals, needs identified by the committee are to

- Improve analytical methods that facilitate rapid testing of products for purity and activity.
- Develop high-resolution protein-purification methods for scaleup and application in the industrial manufacture of ultrapure products.
- Develop process-control technology for integrating biological production sequences into stable and robust automated manufacturing systems.
- Enhance biological and biochemical technology for increasing the efficiency of protein folding and improving the expression of recombinant proteins.

For specialty bioproducts and industrial chemicals, key needs are to

- Develop separation and purification technologies that are specially adapted to the recovery of products from dilute aqueous streams characteristic of materials derived from microbial fermentation, plant cell culture, or whole plant material.
- Develop processing technologies that will facilitate the economical conversion of cellulose-based materials into industrial chemicals and fuels.
- Develop specially adapted or genetically altered microorganisms that can transform biomass materials into industrial chemicals and other products.
- Develop bioproduct manufacturing processes that are controlled and regulated and have predictable performance.

Appropriate bioreactor design and operating conditions must be implemented on scaleup to ensure that product characteristics are maintained, regardless of the type of product. Bioprocess engineers are particularly well suited to integrate bioreaction engineering concepts with the subtleties of cellular metabolism to achieve the necessary product qualities.

Bioprocess-engineering input is important for environmental applications of biotechnology, where the needs are to

- Study the role of microbial interactions in degrading of toxic wastes in the environment and detoxifying industrial wastes at the plant site.
- Define standards by which the effects of bioprocessing in detoxifying wastes will be measured.
- Implement bioprocess-engineering methods in the design of waste-processing technologies.

RECOMMENDATIONS

To meet the global challenges of competition in industrialization of biotechnology and to address national needs, the committee recommends

- A coordinated, long-term plan of research, development, training, and education in bioprocess engineering, with well-defined goals that involve participation of industry, academe, and the federal government.
- A research and educational program in bioprocess engineering that emphasizes cross-disciplinary interactions between scientists and engineers and a multidisciplinary team approach to problem-solving, which has historically been the keystone of success in American industrial development.
- Increased cooperation between industry and the Food and Drug Administration for the express purpose of developing quality-control methods and standards and good manufacturing practices for the manufacture of biotechnology products.

Sustained funding by the federal government is essential to the success of research and education programs for training bioprocess engineers, as is the participation of industry—in planning, training, and supply of physical and financial resources.

The ability of the United States to sustain a dominant global position in biotechnology lies in developing a strong resource base for bioprocess engineering and bioproduct manufacturing and maintaining its primacy in basic life-science research. The United States has made an enormous, and enormously successful, investment in basic biological science. To protect the investment and to capitalize on it, there must now also be an investment in bioprocess engineering.