Biosensing

International Research and Development

by
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A C.I.P. Catalogue record for this book is available from the Library of Congress.

ISBN-10 1-4020-4057-1 (HB)
ISBN-13 978-1-4020-4057-3 (HB)
ISBN-10 1-4020-4058-X (e-book)
ISBN-13 978-1-4020-4058-0 (e-book)

Published by Springer,
P.O. Box 17, 3300 AA Dordrecht, The Netherlands.

www.springer.com

This document was sponsored by the National Science Foundation (NSF) and other agencies of the U.S. Government under awards from the NSF (ENG-0104476) and the Army Research Office (DAAD19-03-1-0067) awarded to the World Technology Evaluation Center, Inc. The government has certain rights in this material. Any opinions, findings, and conclusions or recommendations expressed in this material are those of the authors and do not necessarily reflect the views of the United States Government, the authors' parent institutions, or WTEC, Inc.

Printed on acid-free paper

Printed in the Netherlands.

BIOSENSING

WTEC Panel on International R&D in Biosensing

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Abstract

This report reviews international research and development activities in the field of biosensing. Biosensing includes systems that incorporate a variety of means, including electrical, electronic, and photonic devices; biological materials (e.g., tissue, enzymes, nucleic acids, etc.); and chemical analysis to produce detectable signals for the monitoring or identification of biological phenomena. This is distinct from "biosensors" that employ only biological materials or mechanisms for sensing. In a broader sense, the study of biosensing includes any approach to detection of biological elements and the associated software or computer identification technologies (e.g., imaging) that identify biological characteristics. Topics covered include the national initiatives, interactions between industry and universities, technology and manufacturing infrastructure, and emerging applications research. The panel's findings include the following: Europe leads in development and deployment of inexpensive distributed sensing systems. Europe also leads in integration of components and materials in microfabricated systems. Europe and Japan both have much R&D on DNA array technology, but the impact is likely to be only incremental. The United States leads in surface engineering applied to biosensing and in integration of analog-digital systems. Both Europe's and Japan's communication infrastructures are better suited for networked biosensing applications than those of the United States. Integrated biosensing research groups are more common in Europe and Japan. Additional findings are outlined in the panel's executive summary.

WTEC Mission

WTEC provides assessments of foreign research and development in selected technologies under awards from the National Science Foundation, the Office of Naval Research, and other agencies. Formerly part of Loyola College's International Technology Research Institute, WTEC is now a separate non-profit research institute. Michael Reischman, Deputy Assistant Director for Engineering, is NSF Program Director for WTEC. Sponsors interested in international technology assessments and related studies can provide support for the program through NSF or directly through separate grants to WTEC.

WTEC's mission is to inform U.S. scientists, engineers, and policymakers of global trends in science and technology. WTEC assessments cover basic research, advanced development, and applications. Panels of typically six technical experts conduct WTEC assessments. Panelists are leading authorities in their field, technically active, and knowledgeable about U.S. and foreign research programs. As part of the assessment process, panels visit and carry out extensive discussions with foreign scientists and engineers in their labs.

The WTEC staff helps select topics, recruits expert panelists, arranges study visits to foreign laboratories, organizes workshop presentations, and finally, edits and disseminates the final reports.

Executive Editor: Dr. Marvin Cassman, Former Director, National Institute of General Medical Sciences, NIH

Series Editor: Dr. R.D. Shelton, President WTEC

World Technology Evaluation Center, Inc. (WTEC)

Foreword

> We have come to know that our ability to survive and grow as a nation to a very large degree depends upon our scientific progress. Moreover, it is not enough simply to keep abreast of the rest of the world in scientific matters. We must maintain our leadership.[1]

President Harry Truman spoke those words in 1950, in the aftermath of World War II and in the midst of the Cold War. Indeed, the scientific and engineering leadership of the United States and its allies in the twentieth century played key roles in the successful outcomes of both World War II and the Cold War, sparing the world the twin horrors of fascism and totalitarian communism, and fueling the economic prosperity that followed. Today, as the United States and its allies once again find themselves at war, President Truman's words ring as true as they did a half-century ago. The goal set out in the Truman Administration of maintaining leadership in science has remained the policy of the U.S. Government to this day: Dr. John Marburger, the Director of the Office of Science and Technology (OSTP) in the Executive Office of the President made remarks to that effect during his confirmation hearings in October 2001.[2]

The United States needs metrics for measuring its success in meeting this goal of maintaining leadership in science and technology. That is one of the reasons that the National Science Foundation (NSF) and many other agencies of the U.S. Government have supported the World Technology Evaluation Center (WTEC) and its predecessor programs for the past 20 years. While other programs have attempted to measure the international competitiveness of U.S. research by comparing funding amounts, publication statistics, or patent activity, WTEC has been the most significant public domain effort in the U.S. Government to use peer review to evaluate the status of U.S. efforts in comparison to those abroad. Since 1983, WTEC has conducted over 50 such assessments in a wide variety of fields, from advanced computing, to nanoscience and technology, to biotechnology.

The results have been extremely useful to NSF and other agencies in evaluating ongoing research programs, and in setting objectives for the

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[1] Remarks by the President on May 10, 1950, on the occasion of the signing of the law that created the National Science Foundation. *Public Papers of the Presidents* 120: p. 338.

[2] http://www.ostp.gov/html/01_1012.html.

future. WTEC studies also have been important in establishing new lines of communication and identifying opportunities for cooperation between U.S. researchers and their colleagues abroad, thus helping to accelerate the progress of science and technology generally within the international community. WTEC is an excellent example of cooperation and coordination among the many agencies of the U.S. Government that are involved in funding research and development: almost every WTEC study has been supported by a coalition of agencies with interests related to the particular subject at hand.

As President Truman said over 50 years ago, our very survival depends upon continued leadership in science and technology. WTEC plays a key role in determining whether the United States is meeting that challenge, and in promoting that leadership.

Michael Reischman
Deputy Assistant Director for Engineering
National Science Foundation

PREFACE

This report was prepared by the World Technology Evalutation Center (WTEC), a nonprofit research institute funded by grants and other awards from most of the Federal research agencies. Among other studies, WTEC has provided peer reviews by panels of U.S. experts of international research and development (R&D) in more than 55 fields since 1989. In 2002, WTEC was asked by several agencies to assess international R&D in biosensing. This report is the final product of that study.

We would like to thank our distinguished panel of experts, who are the authors of this report, for all of their efforts to bring this study to a successful conclusion. We also are very grateful to our foreign hosts for their generous hospitality, and to the participants in our preliminary workshop on U.S. biosensing R&D. Of course, this study would not have been possible without encouragement from our sponsor representatives: Bruce Hamilton, Fred Heineken, Elbert Marsh, Deborah Young, Fil Bartoli, and Vijay Jain of the National Science Foundation (NSF); Christine Kelley, Joan Harmon, Dick Swaja, Mollie Sourwine, and Stephen Green of the National Institutes of Health (NIH); John Hines and Steve Davison of the National Aeronautics and Space Administration (NASA); Dan Schmoldt of the U.S. Department of Agriculture (USDA); and Micheline Strand of the U.S. Army Research Office (ARO).

This report covers a broad spectrum of material on the subject, so it may be useful to give a preview here. The Executive Summary was prepared by the chair, Jerome Schultz, with input from all the panelists. The chapters in the body of this report present the panel's findings in an analytical organization by subdiscipline. Appendix A provides the biographies of the panelists. Appendices B and C contain the panel's individual reports on each site visited in Europe and Japan, which form a chronological or geographic organization of much of the material. Appendices D-H present information on U.S. Government sponsored projects in the field. Appendix I presents biosensing program information from the European Union 6th Framework Programme (2002–2006). Appendix J lists recent biosensing-related patents filed by organizations that hosted the panel's site visits in Europe and Japan.

To complement the qualitative assessment by peer review, Appendix K is a quantitative bibliometric study of international biosensors research for 1997-2002. This work was performed by Grant Lewison of the City University, London, for WTEC. Finally, a glossary is provided as Appendix L.

All the products of this project are available at http://www.wtec.org. The full-color electronic version of this report is particularly useful for viewing some of the figures that do not reproduce well in black and white. Also posted at this site are the slideshows from two workshops held for this project, which contain considerable additional information on biosensing R&D in the United States and abroad.

Roan Horning
WTEC, Inc.

Executive Summary

Jerome S. Schultz

The long-standing U.S. national interest in biosensing has encompassed broad requirements for reliable and sensitive sensing systems for medical diagnostics, environmental monitoring, and food safety assurance. National demands on biosensing systems have expanded and taken on a new urgency in the wake of the September 11, 2001, terrorist attacks and the anthrax attacks that followed.

In a broad sense, the study of biosensing includes any approach to detection of biological elements and the associated software or computer identification technologies (e.g., imaging) that identify biological characteristics. *Biosensing systems* incorporate a variety of means, including electrical, electronic, and photonic devices; biological materials such as tissue, enzymes, and nucleic acids; and chemical analysis, to produce detectable signals for the monitoring or identification of biological phenomena. This is distinct from *biosensors* that employ only biological materials or mechanisms for sensing. Biosensing is finding a growing number of applications in a wide variety of areas, including biomedicine; food production and processing; and detection of bacteria, viruses, and biological toxins for bio-warfare defense.

In late May 2002, the World Technology Evaluation Center (WTEC) embarked on a study to assess research and development activities related to biosensing in the United States and worldwide, under the sponsorship of the National Science Foundation (NSF), the National Institutes of Health (NIH), the United States Department of Agriculture (USDA), the National Aeronautics and Space Administration (NASA) and the Army Research Office (ARO). The goals of this study are to gather information and disseminate it to government decisionmakers, the research community, and the public on worldwide status and trends in biosensing R&D, and to critically analyze and compare the research in the United States with that being pursued in Japan, Europe, or other major industrialized countries. The information gathered through this study is intended to serve the purposes of identifying good ideas worth exploring in U.S. R&D programs; clarifying research opportunities and requirements for progress in the field; identifying opportunities for international collaboration; and evaluating the position of foreign research programs relative to those in the United States.

To achieve these goals, WTEC recruited a panel of seven experts in the field (see biographies in Appendix A) to carry out a series of three major tasks designed to deliver the maximum amount of quality information to the sponsors and the public within the constraints of time and resources:

1. Host a workshop of members of the U.S. biosensing R&D community to characterize the state of the art and current trends in biosensor technologies in the United States. [The WTEC Biosensing Study U.S. R&D Overview Workshop was held at NIH in Bethesda, MD, on 3–4 December 2002.]
2. Conduct site visits to gather first-hand information from many of the world's best university and industrial laboratories in biosensing research. [The WTEC panelists conducted site visits to laboratories in Europe, Australia, and Japan during January and March 2003.]
3. Report back findings in both a public forum and in writing to the U.S. sponsors, the scientific community, and the public at large. [The WTEC Workshop on Biosensing in Europe, Japan, and the United States was held on 13 May 2003 at the Bethesda, MD, Marriott Hotel.]

This report, the final phase of the study, details and analyzes the results of the WTEC biosensing panel's literature review, U.S. survey, and Europe and Japan site visits. It is available to the public on the Web at www.wtec.org/biosensing, as well as in print.

PRINCIPAL FINDINGS

Infrastructure

Biosensing research has exploded dramatically in recent years. Both NIH and NSF sponsored over 200 projects related to biosensing in 2002. Appendixes D and E lists these projects as examples of ongoing research, ranging from surface chemistry to intelligent agents, and Appendixes F-H give an insight into the depth and breadth of work funded by the Defense Advanced Research Projects Agency (DARPA), ARO, and the Department of Energy (DOE).

Expansion of research activity has been facilitated by major technological breakthroughs in the fields of microelectronics, microfabrication, surface science, photonics, and information sciences. In current terminology, "Bio-Nano-Info" has become a new paradigm for the convergence of research in the fields of biotechnology, nanotechnology, and information technology. In the United States, NSF has recognized this trend of connecting bio-nano-info in its report, *Converging Technologies* *for Improving Human Performance* (Roco and Bainbridge 2003). Further evidence for the overlap of fields are DARPA programs in BioComputational Systems, Bio-Molecular Microsystems (SIMBIOSYS), and Nanostructure in Biology.

Because of this technological convergence, it is difficult to separate out the human, technical, and financial resources that are being allocated to biosensing systems alone. Along with the multidisciplinary nature of the science advancing biosensing R&D, it is clear that Japan and Europe are increasingly building collaborative efforts to carry out biosensing projects; in some cases the teams are industrial/academic; in others, government/academic. It also appears there is an escalating interest in commercialization of biosensing technologies, and several large new biosensing-related R&D facilities are being built. A manifestation of these infrastructure trends is seen in various program initiatives in the United States, Europe, and Japan.

In Europe, an indicator of future goals and plans for research is provided by the EU's Sixth Framework Programme solicitations for 2002–2006 (see summary in Appendix I). Although, this framework document does not explicitly identify biosensing technologies as a program element, one can find references to biosensing systems under these program areas:

- Life Sciences, genomics, and biotechnology for health
- Information Society technologies
- Nanotechnologies and nanosciences, knowledge-based multifunctional materials, and new production processes and devices

The projected budget for these topics is about $7 billion, and about $1 billion of these funds will probably relate directly to biosensing systems.

Another feature of the European approach to building a research and commercial capability relating to biosensing products is the organization of collaborative partnerships between academic research centers and companies. For example, in the Berlin-Brandenburg region there are three Max Planck Institutes and two Fraunhofer Institutes located near the University of Potsdam that actively work on several collaborative projects. There are approximately 100 companies in this consortium with interests in diagnostics, biotechnology, and software that will accelerate the transfer of biosensing systems into the marketplace.

In Japan, the universities the WTEC panel visited all had programs relating biotechnology, nanotechnology, and computers. For example, the fields of interest stated by the President of the Tokyo University of Agriculture and Technology are (1) Biotechnology, (2) Information and Communications Technologies, (3) Environmental Science and Resource Science, and (4) Nanotechnology. This university has an extensive program of providing incubator facilities to promote technology transfer from the university to industry.

WTEC visits to various universities confirmed that a major change is underway in the ability of universities in Japan to interact with industry, as many state-owned institutions will be released from central government control in the next few years. This has resulted in a significant increase in patent application activity by Japanese faculty. Another example of the trend for the direct connection of university and corporate research is the new School of Bionics at the Tokyo University of Technology. A new US$250 million building with 15,000 m^2 of space opened in April 2003 to house industrial/academic research projects along with the traditional academic research and academic facilities. Four floors of the new facility were to be occupied by corporate research laboratories who will co-sponsor research in the institute. The university also plans to have a degree program in technology management.

There is extensive collaboration in Japan between government laboratories and academia. Visits to government laboratories indicate significant national spending, despite Japanese economic hardship. This suggests acceptance of the idea that technology is essential for future economic success.

To complement the WTEC panel's literature review, public forums, and first-hand observations of international biosensing research and development, this report includes in Appendix K a bibliometric study of international biosensors research in the period 1997–2002 that underscores the high activity in this field based on the number and quality of published biosensor studies in this period, particularly in the United States, Europe, and Japan.

Table ES.1 summarizes the key observations by the WTEC panel concerning the patterns of infrastructure development for biosensing in the United States, Europe, and Japan, to highlight the unique approaches and relative strengths of these regions.

TECHNOLOGY HIGHLIGHTS FROM SITE VISITS

In two separate, one-week rounds of visits in early 2003, the WTEC panel toured 40 premier research establishments in Europe, Australia, and Japan that have a focus or known activities in biosensing and related areas. These visits included universities, industry laboratories, and government research centers: 23 facilities in Europe and Australia, and 17 in Japan. The capabilities listed below reflect not a detailed analysis but rather highlights of first-hand interviews and observations of programs in the laboratories the panel visited. Site reports are included in Appendix B (Europe and Australia) and Appendix C (Japan) of this report.

Table ES.1
Comparative Patterns in Funding of Biosensing R&D and Commercialization, by Region†

	United States	Europe	Japan
Research Focus	**Fundamental science: Academia,** national labs **Applied science & engineering: small companies, national labs,** large companies	**Applied Science & engineering: academia**, national labs, small & large companies	Fundamental science, engineering
Teaming mechanisms	Individual investigators, interdisciplinary interactions	**Multidisciplinary teams**	Individual investigators, interdisciplinary teams
Types of collaboration	International collaborations	**Multinational teams**, major EU support	**National focus**
Support for new technology areas	**Federal support to open new technology areas: MEMS, microfluidics, nanotechnology**	Generally follow U.S. lead into new technology areas	Generally follow U.S. lead, but **industry has a longer time horizon** than the U.S.
Academic support for applications focus in R&D	Nonuniform support	**Strong support**	Widespread support
Support for technology transfer to industry, commercialization	Federal government, **individual entrepreneur, venture* support**	**Local government support**, national government support, **academic admin. support**	National government support and **increasing university emphasis**

† Bold indicates particular strength /emphasis
* In good economic times

Europe

- Highly automated 2D-gel ICAT (mass spectrometry) techniques are used to carry out high-throughput protein analysis at Oxford GlycoSciences (Dr. Christian Pohlff).
- A combination of lab-on-a-chip technologies and mass spectroscopy are used to tackle the challenging characterization of the proteome at the University of Twente, MESA+ Institute (Professor David Reinhoudt).
- Live cell analysis with the Biacore Procel fluorescence detection/microfluidic system is well established at Biacore in Uppsula, Sweden.
- Reflectometric interference spectroscopy is used for low-cost and highly miniaturized biosensing arrays at the Institute of Physical and Theoretical Chemistry, University of Tübingen (Professor Gunter Gauglitz).
- Low-energy electron point-source (LEEPS) microscopy appears to be leading towards resolutions of features below 1 nm at Ruprecht-Karls University Heidelberg (Professor Michael Grunze).
- Lipid bilayer vesicles and lipid nanotube-vesicle-networks are being investigated for encapsulation and support of reconstituted biological functions such as receptors, synaptic vesicles, and signal-transduction systems/pathways at Linköping University (Professor Ingemar Lundstrom).

Japan

- Uniform, nano-sized (50–100 nm), lipid-covered (containing fusion proteins) ferromagnetic particles produced by *magnetospirillium magneticum* are used as unique components of biosensors at Tokyo University of Agriculture and Technology, Department of Biotechnology and Life Science (Professor Tadashi Matsunaga).
- Ferrocenyl napthalene diimide (FND) is being used as a DNA hybridization indicator to enable charge transfer to microelectrodes producing an electrochemical signal proportional to the amount of target DNA at Kyushu University (Professor Shigeori Takanaka).
- Confocal microscopic imaging of molecular events in single living cells is being achieved by protein constructs of biorecognition molecules with fluorescent proteins at the University of Tokyo, Department of Chemistry (Professor Yoshi Umezawa).
- A thermal lens microscope technique has been perfected to measure concentrations in the zepto-mole range, or about 50–100 molecules,

on biochips at the School of Engineering, University of Tokyo (Professor T. Kitamori).

- Novel methods are being used to synthesize photo-induced electron transfer (PET) of organic species that are incorporated in the design of new sensing materials at the Graduate School of Pharmaceutical Sciences, University of Tokyo (Professor Kazuya Kikuchi).

COMPARATIVE REGIONAL STRENGTHS IN KEY BIOSENSING AREAS

The WTEC panel collected a vast amount of information from a preliminary literature review, the initial U.S. workshop, site visits to Europe and Japan, and the final workshop to report on and receive feedback from the research community about the study findings. Based on this information, the panel has made a comparative assessment of the status of biosensing research in Europe and Japan relative to that in the United States. Table ES.2 compares for each of the key areas of biosensing that are discussed in chapters 2 through 7 the panel's evaluation of the knowledge bases, work to date/in progress, and the relative approaches/strengths of the worldwide biosensing field generally, with a summary assessment of which region(s) lead the area.

Table ES.2.
Comparison of U.S., Japanese, and European R&D Activities in Biosensing

Area	Subarea	Topic	Knowledge Base	Work to Date	Leading Region
Optical Biosensing (see Chapter 2)		Arrays	Patterning Surface chemistry	Extensive, mature	U.S.
		Interfer-ometric, label-free	Surface plasmon resonance Interference	Old method, but ongoing efforts	Europe
		Cheap, distributed sensors	Screen printing Optical transduction	New and promising	Europe