chapter 10

Bioelectronics

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Introduction

The potential for the use of proteins in electronic dmices has received attention recently with the advent of recombinant DNA (rDNA) technology}' and the potential for computer-aided design of proteins (I ,2,3 5 ,6,7, 11, 13,14,15,19,2 1). Work is focused in two areas: biosensors and biochips. Biosensors (biological}' based sensors) have been used for several years, but design problems have limited their acceptance. Biotechnology is expected to increase the variety, stability, and sensitivity of these devices. Biochips (biologically based microchips) capable of logic and memory are still only speculative, and their development is many years away.

Biosensors

A potential application of biotechnology is in the development of improved sensing devices. Because of their high specificity for given substances, enzymes and monocIonal antibodies (hlAbs) are particularly suited for use as sensors. Sensors using these biological molecules have the potential to be smaller and more sensitive than traditional sensors.

Biosensors using enzymes have been used to detect the presence of various organic compounds for many years (12). Most of them have used a free or immobilized enzyme and an ion-sensitive electrode that measures indirectly (e.g., by temperature or color changes produced during an enzymatic reaction) the presence of a product the formation of which is catalyzed by the enzyme. Because of the proximity of the enzyme and electrode, these biosensors are rapid and sensitive. They have not had wide application, however, because of the high cost of many enzymes, lack of particular enzymes, and temperature instability.

The use of rDNA and MAb technology and computer-aided design of enzymes and other proteins may allow the problems associated with existing biosensors to be overcome. The cloning in bacteria of genes coding for useful enzymes, for example, could allow the enzymes to be made in large amounts cost effectively. The use of MAbs, which can be made for virtually any molecule, not only could obviate the need for enzymes but also could substantially broaden the applications of biosensors. A longer term solution to the lack of particular enzymes might be to have computers design enzymes with particular catalytic functions. Finally, features of proteins that determine temperature stability could be incorporated into the genes that code for important sensing enzymes.

A new approach to fabrication is yielding biosensors with greater speed, sensitivity, and ease of operation [4). The new biosensors use a field-effect transistor that translates a chemical reaction, such as that catalyzed by an enzyme, into an electronic signal. Because the electronic response is a direct measure of the chemical reaction, the sensitivity and speed of the device is increased. (It is postulated that these sensors could use MAbs as specific detection agents.) The British Government has one of these new biosensors on the market; it detects a particular nerve gas (4).

There are many potential applications for improved biosensors in the medical, industrial, environmental, and defense fields **(2, 12).** These are discussed in turn,

In medical diagnostics, many substances need to be measured accurately and rapidly, but the sensors now available are often expensive, slow, and insensitive. Improved biosensors could potentially solve many or all of these problems. Such biosensors could detect, for example:

- antigens associated with infectious disease,
- hormonal levels to examine endocrine function, and
- serum protein levels indicative of disease.

One particularly important medical application of improved biosensors could be in the treatment of diabetic patients for whom proper levels of insulin and glucose must be maintained. Small, implantable devices that sample blood for glucose and regulate the delivery of insulin could be developed.

As mentioned in ***Chapter 3: The Technologies,*** one of the hindrances to effective bioprocess monitoring and control is the need for a wide range of sterilizable sensors. Biosensors could be developed to measure levels of key reaction substances, such as reactants, intermediates, nutrients, and products. Continuous monitoring of several substances with biosensors interfaced to a computer would allow better control over the reaction process and thus increase productivity. The use of thermotolerant enzymes could potentially allow these sensors to be sterilized in place.

A potential environmental application of improved biosensors would be to monitor water and air quality. However, cost considerations limit the use of the extremely sensitive sensors now available. Additionally, very few measuring systems are portable enough for monitoring in the field. Better biosensors might circumvent these problems. other environmental biosensors could be developed to detect exposure of workers to hazardous substances and to monitor indoor air pollution in the office or at home.

The U.S. Department of Defense (DOD), in the near future, will be the major supporter of biosensing research in the United States ($8 million over the next 4 years). DOD's aim is to develop biosensors for the detection of chemical and biological warfare agents that are small, have high sensitivity, quick response times, and no false alarms (18). If such devices were developed, they would have broad civilian applications such as those just mentioned. Companies funding research on biosensors for a number of uses include IBM, IT&T, and Johnson & Johnson in the United States and Cambridge Life Sciences in the United Kingdom (4,9,16).

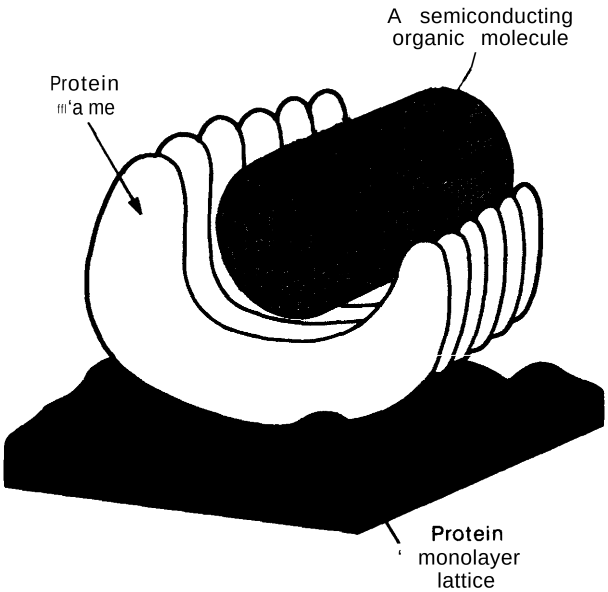
Many technical barriers to developing highly reliable biosensors remain (8,17). Operating limitations (e.g., a narrow temperature range) and fabrication problems have yet to be overcome. Research is needed to identify which proteins are most appropriate for this technology. Moreover, sensors implanted in animals or used to monitor bioprocesses must be sterilized prior to implantation or use, and research is needed to develop biosensors that are not destroyed by sterilization methods. Over the next 5 to 10 years, many of these generic problems inherent in the development of biosensors will probably be solved (2,18).

Biochips

Probably the most novel potential application of biotechnology is in the production of a bimolecular electronic device. Such a device would contain a specially designed organic molecule that would act as a semiconductor surrounded and stabilized by specially designed proteins, as shown in figure 29. Researchers have studied the use of proteins as a matrix for semiconductors since the early 1970's, but the possibility of designing proteins aided by computers and producing the proteins with rDNA technology has sparked more intense interest.

Two small entrepreneurial firms in the United States are doing research on biological microchips, or biochips: Gentronix (Rockville, Md.) and Ean-Tech (San Francisco, Calif.). Furthermore, DOD will be funding biochip research beginning in fiscal year 1984 at $3 million to $4 million for 5 years. A few large electronics companies in the United States (Westinghouse, General Electric, and IBM) have small inhouse programs in this area. Japan, France, the United Kingdom, and the U.S.S.R. have indicated interest in bimolecular computers (10,20).

Figure 29.—The Use of Proteins in Constructing a Circuit



SOURCE Otflce of Technology Assessment

Bioelectronics research is in its infancy. Although most potential applications of proteins in this field are only speculative, the successful development of these applications could have a substantial effect on the electronics industry. Computers using protein-based biochips, for example, would be smaller, faster, more energy efficient, and possibly more reliable than computers using silicon chips. * The impact of such biochips would be as broad as that of present computers, from hand-held calculators to robotics.

The biological nature of biochips also raises the possibility of some exciting medical applications– they could be implanted in the body to interface with the living system. Some possibilities include:

- brain implants to circumvent damage that has caused blindness and deafness,
- cardiac implants to regulate heart beat,
- blood implants to regulate drug delivery (e.g., insulin for diabetics), and
- implants to control artificial limbs.

DOD considers biochip technology potentially very useful. Because the circuits would be the width of molecules, the resulting devices would be very small and should find use in areas where small size is essential (e.g., in missile guidance). Furthermore, because of the nonmetallic nature of biochips, it is thought that they would be immune to '(electromagnetic pulse," the extraordinary electrical charge that results from a nuclear explosion and renders useless all metallic devices in a large area. In spite of the potential uses, however, it is likely to be many years before any complex biochip will be developed.

A conventional silicon chip contains a set of optically imprinted circuits on a wafer of silicon. Four factors limit the number of circuits contained on a chip, First, the lower limit of the width of a circuit is determined by the wavelength of light used for imprinting. The current limit is 1 to 10 microns; it has been postulated that by 1990 the width could be 100 times narrower (2). Second, the distance between circuits is limited by the nature of the silicon circuit construction itself. When circuits are too close together, electrons can "tunnel" between circuits. This tunneling decreases the reliability of the electronic device. The lower limit for the distance between circuits is rapidly being approached for silicon chips. The third limiting factor for conventional chips is heat dissipation. As circuits are packed more closely together, the chip becomes too hot to function effectively. Lastly, as the amount of information processing ability per chip increases, the problems with fabrication and quality control increase.

Biological and chemically synthesized molecules conceivably could solve these problems associated with conventional silicon chips as well as provide additional advantages in design. Because the molecules themselves would be the conductors, the lower limit of the circuit width would be the width of molecules, which is several orders of magnitude narrower than silicon circuits used (or even postulated) at present. Molecular circuits could be placed very close to one another without tunneling effects, because the proposed molecules conduct current without losing electrons. Furthermore, since almost no energy is required for molecules to conduct current, very little heat would be generated even when the circuits were close together. The specificity of complex interactions among proteins and the self-assembling

*Mutations that occur at a certain low level during growth of micro-organisms could affect the reliability of the final product.

processes characteristic of biological systems would facilitate the fabrication of very reliable biochips.

The fabrication of complex three-dimensional biochips with the fabrication technology now used in the electronics industry is probably impossible. An essential feature of the use of a protein matrix is that the proteins direct their own assembly and the appropriate positioning of the semiconductor molecules. There are numerous examples of self-assembling protein structures, including virus particles, and these are being studied intensely for potential applications to biochip technology.

Several proteins, including MAbs, have been suggested for constructing a biochip in three dimensions. The movement of microelectronics from two- to threedimensional structures would allow not only for increased complexity but also for greatly reduced size. The use of a three-dimensional protein matrix necessitates the design of proteins that will interact with other proteins at correct and unique angles. The construction of these proteins will rely on computer-aided design and rDNA technology.

There are many problems to be solved before a threedimensional biochip will become available. Biological equivalents of capacitors, transistors, and resistors are yet to be developed. Switching devices, necessary for use with the computer binary system, are only theorized. No one has determined how a three-dimensional biological structure will do logic functions or store memory. The problem of interfacing biochips so they can be programed or can assimilate other input has not been addressed. And, because the chips would use complex molecules, research needs to be done on their environmental stability,

Biochips will not be possible without computer-designed proteins and rDNA technology. Yet it will probably be several years before rDNA technology will be able to contribute substantially to biochip research, because it is first necessary to understand more about the relationship between protein structure and function, the biological self-assembly processes, and the mechanisms by which molecules could do logic functions and store memory.

Priorities for future research

Increased funding for research in the following areas could speed the development of bioelectronics:

- computer-aided design of proteins,
- temperature stability of proteins,
- field-effect transistors,
- miniaturization of sensors,
- biological self-assembly processes, and
- molecular-switching mechanisms for electronic signal propagation.

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