Protein-Based Computers

Devices fabricated from biological molecules promise compact size and faster data storage. They lend themselves to use in parallel-processing computers, three-dimensional memories and neural networks

by Robert R. Birge

The world's most advanced supercomputer does not require a single semiconductor chip. The human brain consists of organic molecules that combine to form a highly sophisticated network able to calculate, perceive, manipulate, self-repair, think and feel. Digital computers can certainly perform calculations much faster and more precisely than humans can, but even simple organisms are superior to computers in the other five domains. Computer designers may never be able to make machines having all the faculties of a natural brain, but many of us think we can exploit some special properties of biological molecules—particularly proteins—to build computer components that are smaller, faster and more powerful than any electronic devices on the drawing boards thus far.

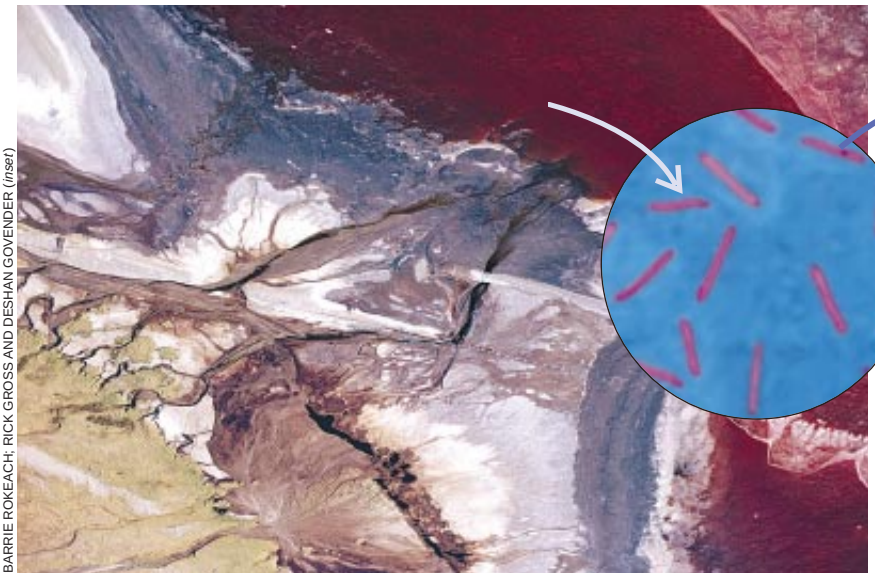
The size issue is especially pressing. Since the 1960s the computer industry has been compelled to make the individual components on semiconductor chips smaller and smaller in order to manufacture larger memories and more powerful processors economically. These chips essentially consist of arrays of switches, usually of the kind known as logic gates, that flip between two states—designated as 0 and 1—in response to changes in the electric current passing through them. (Computers typically represent all information in terms of such binary digits, or bits.) If the trend toward miniaturization continues, the size of a single logic gate will approach the size of molecules by about the year 2030.

But there is a serious roadblock. Each factor of two in miniaturization increases the cost of manufacturing a chip by a factor of five. At some point the search for ever smaller electronic devices may be limited by economics rather than physics [see "The Wall," by Gary Stix, "Science and Business," SCIENTIFIC AMERICAN, July 1994]. On the other hand, the use of biological molecules as the active components in computer circuitry may offer an alternative approach that is more economical.

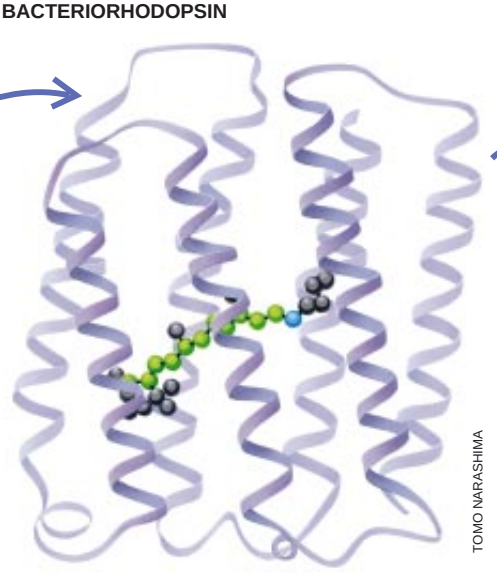
Molecules can potentially serve as computer switches because their atoms are mobile and change position in a predictable way. If we can direct that atomic motion and thereby consistently generate at least two discrete states in a molecule, we can use each state to represent either 0 or 1. Such switches offer reductions in the size of hardware because they are themselves small—about one thousandth the size of the semiconductor transistors used today as gates (which measure about one micron, or a millionth of a meter, across). Indeed, a biomolecular computer could in principle be one fiftieth the size of a present-day semiconductor computer composed of a similar number of logic elements. In the computer business, smaller gate size generally makes for a faster device, and protein-based computers could theoretically operate 1,000 times faster than modern computers.

At this stage no one is seriously proposing a purely biomolecular computer. Far more likely, at least for the near future, is the use of hybrid technology in which molecules and semiconductors are used in combination. Such an approach should provide computers that are one fiftieth the size and as much as 100 times faster than current ones.

Biological molecules also appeal because they can be designed one atom



BARRIE ROKEACH; RICK GROSS AND DESHAN GOVENDER (*inset*)



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at a time—giving engineers the control they need to manufacture gates able to perform exactly as an application requires. Further, bioelectronic computers should help in the ongoing pursuit of more adaptable computers. Computer scientists are already enhancing the versatility of electronic devices by developing new configurations of computer hardware known as architectures.

Researchers have introduced parallel-processing architectures, which allow multiple sets of data to be manipulated simultaneously. In order to expand memory capacities, they are devising hardware that stores data in three dimensions instead of the usual two. And scientists have built neural networks that mimic the learning-by-association capabilities of the brain, an ability necessary for significant progress toward artificial intelligence. The ability of certain proteins to change their properties in response to light should simplify the hardware required for implementation of these architectures.

Although no computer components made entirely or partly from proteins are on the market yet, ongoing international research efforts are making exciting headway. It seems reasonable to predict that hybrid technology combining semiconductor chips and biological molecules will move from the realm of science fiction to commercial application fairly soon. Liquid-crystal-display technology offers a prime example of a hybrid system that has achieved commercial success. Most laptop computers today depend on liquid-crystal displays, which combine semiconductor devices and organic molecules to control the intensity of the image on screen.

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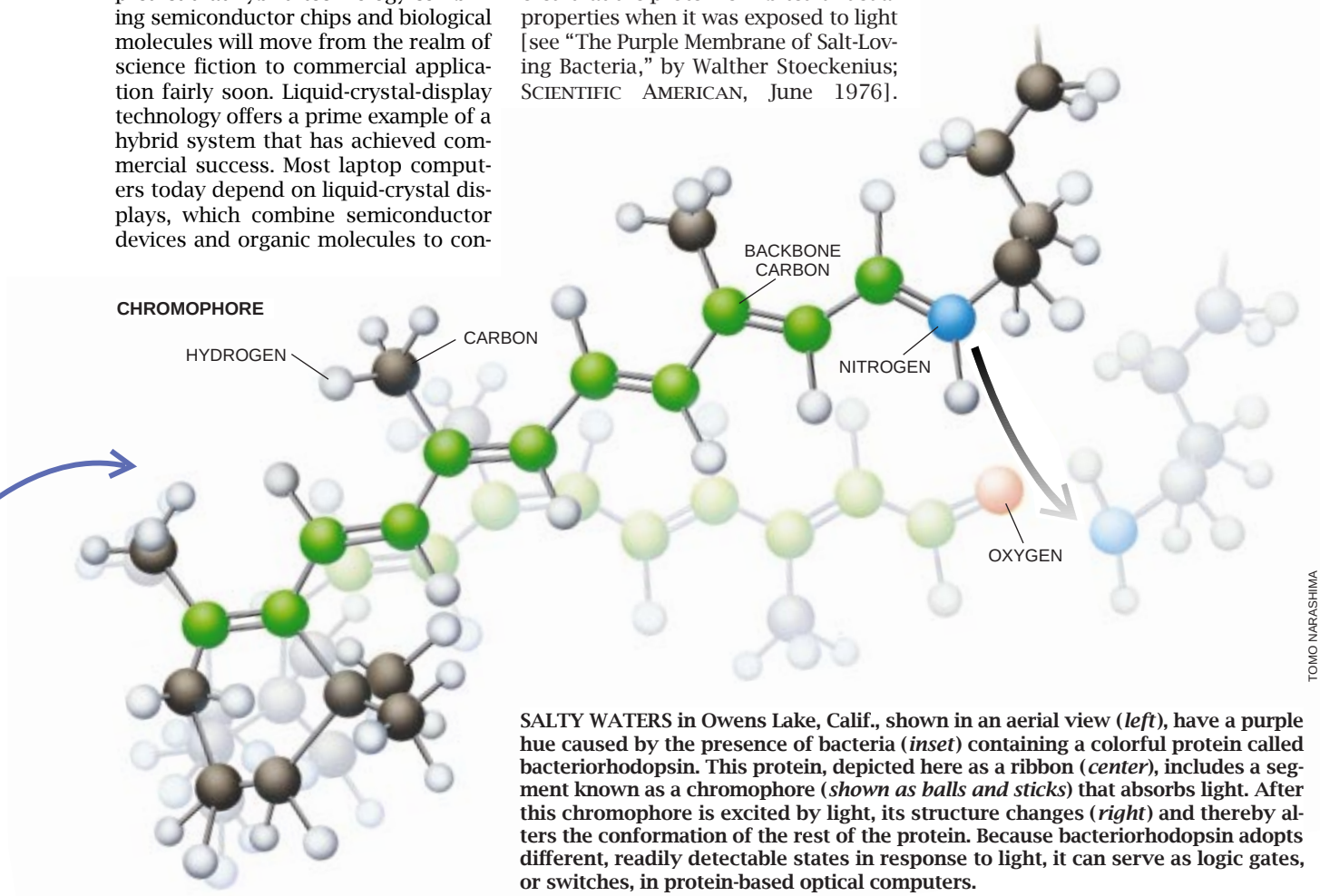
Several biological molecules are under consideration for use in computer hardware, but the bacterial protein bacteriorhodopsin has generated the most interest. During the past 10 years, my laboratory and others in North America, Europe and Japan have built prototype parallel-processing devices, three-dimensional data storage hardware and neural networks based on this protein.

Origins in the Salt Marsh

Interest in bacteriorhodopsin dates back to the early 1970s, when Walther Stoeckenius of the University of California at San Francisco and Dieter Oesterhelt, now at the Max Planck Institute for Biochemistry in Martinsried, discovered that the protein exhibited unusual properties when it was exposed to light [see "The Purple Membrane of Salt-Loving Bacteria," by Walther Stoeckenius; SCIENTIFIC AMERICAN, June 1976]. Found in the membrane of *Halobacterium salinarium,* bacteriorhodopsin enables the bacterium to grow when the concentration of oxygen is insufficient to otherwise sustain the organism. When struck by light, the protein changes its structure and transports a proton across the membrane, thereby supplying energy to maintain cell metabolism.

Soviet scientists were the first to recognize and develop the potential of bacteriorhodopsin for computing. Soon after it was discovered, the late Yuri A. Ovchinnikov of the Shemyakin Institute of Bioorganic Chemistry in Moscow assembled a team of scientists from five Soviet institutions to work on biomolecular electronics as part of what came to be called Project Rhodopsin. Ovchinnikov obtained a good deal of funding



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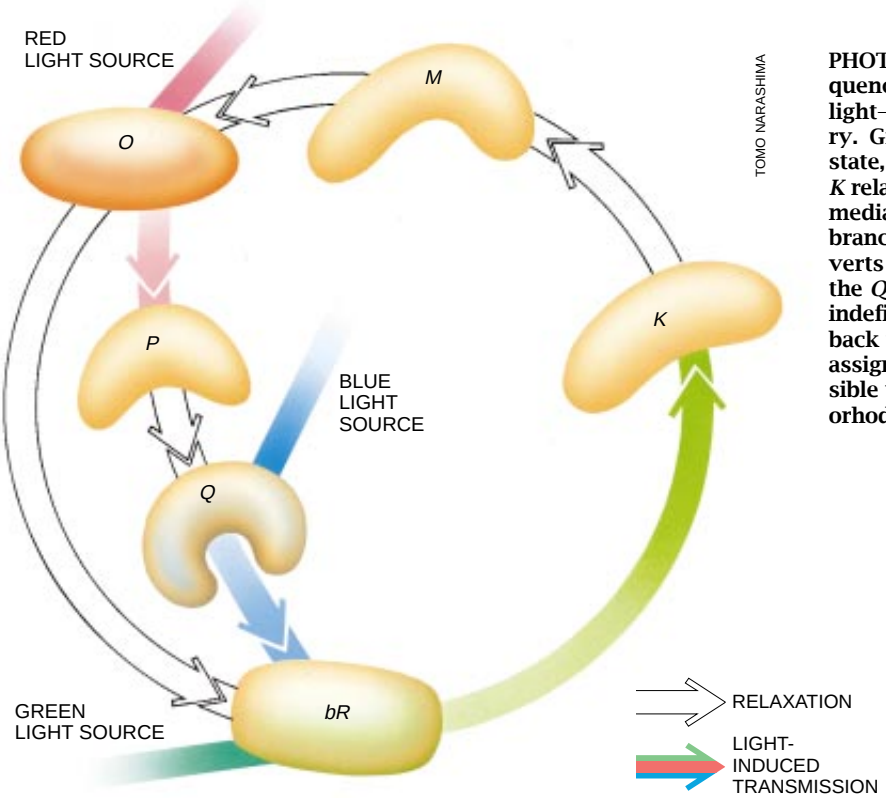
SALTY WATERS in Owens Lake, Calif., shown in an aerial view (*left*), have a purple hue caused by the presence of bacteria (*inset*) containing a colorful protein called bacteriorhodopsin. This protein, depicted here as a ribbon (*center*), includes a segment known as a chromophore (*shown as balls and sticks*) that absorbs light. After this chromophore is excited by light, its structure changes (*right*) and thereby alters the conformation of the rest of the protein. Because bacteriorhodopsin adopts different, readily detectable states in response to light, it can serve as logic gates, or switches, in protein-based optical computers.



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PHOTOCYCLE of bacteriorhodopsin—the sequence of structural changes induced by light—allows for the storage of data in memory. Green light transforms the initial resting state, known as *bR*, to the intermediate *K*. Next *K* relaxes, forming *M* and then *O*. If the *O* intermediate is exposed to red light, a so-called branching reaction occurs. Structure *O* converts to the *P* state, which quickly relaxes to the *Q* state—a form that remains stable almost indefinitely. Blue light, however, will convert *Q* back to *bR*. Any two long-lasting states can be assigned the binary value 0 or 1, making it possible to store information as a series of bacteriorhodopsin molecules in one state or the other.

for such research because he had the ear of Soviet military leaders and was able to convince them that by exploring bioelectronics, Soviet science could leapfrog the West in computer technology.

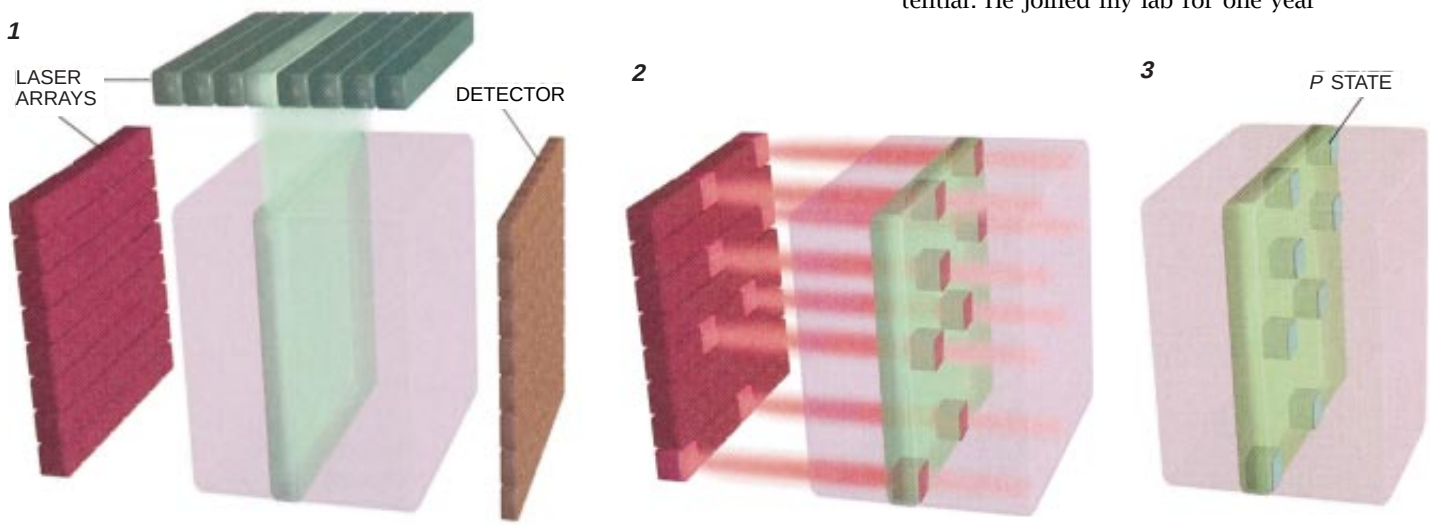
Many aspects of this ambitious project are still considered military secrets and may never be revealed. We do know that the Soviet military made microfiche films, called Biochrome, out of bacteriorhodopsin. Informal reports from former Soviet scientists now in the U.S. indicate that researchers there also made optical data processors using protein technology. The details of their most impressive accomplishment, a processor for military radar, remain obscure.

I became interested in bacteriorhodopsin in the 1970s, while I was studying the biochemical basis of vision at the University of California at Riverside. My work had initially focused on a related protein, rhodopsin, present in the retina of mammals. Both rhodopsin and bacteriorhodopsin are complex proteins that include a light-absorbing component known as a chromophore. The chromophore absorbs energy from light, triggering a complex series of internal motions that result in dramatic changes in the structure of the larger protein. These changes alter the protein's optical and electrical characteristics. For example, when rhodopsin absorbs light in the human eye, the change in structure releases energy that serves as an electrical signal able to convey visual information to the brain.

Computer Applications

At first I was concerned purely with understanding how such light-activated changes to rhodopsin occurred. During the late 1970s, however, I became interested in bacteriorhodopsin as well. I had also decided to apply my knowledge of its properties to the design of computer memories and processors based on the protein. Albert F. Lawrence, then at Hughes Aircraft Company, played an important role in convincing me that bioelectronics had potential. He joined my lab for one year

WRITING DATA



WRITING OF INFORMATION into cubes of bacteriorhodopsin (*purple*), and reading out of that information, is accomplished with laser beams. The writing process is begun by firing green laser beams through a plane of the cube (*1*); this step begins the protein's photocycle. Then, red lasers are fired (*2*) at the particular set of molecules in the plane (*green*) to be converted to the binary 1 state; the remaining molecules represent binary 0. The targeted molecules first form the *P* state (*3*),

to explore the use of biological materials in optical memories.

We focused on bacteriorhodopsin instead of rhodopsin because of the former's greater stability and better optical properties. Also, it can be prepared in large quantities. The components of computers must be able to withstand changes in their environment without breaking apart. Bacteriorhodopsin naturally functions in salt marshes where temperatures can exceed 150 degrees Fahrenheit and where the molecule is often exposed to intense light.

The applications under study for computer processors and the memories on which they operate exploit what is called the photocycle—the series of structural changes bacteriorhodopsin undergoes in response to light. (In its resting state the molecule is known as *bR,* and each intermediate in the series is identified by a letter of the alphabet.) The various intermediates can be used to represent bits of data.

Moreover, the intermediates absorb light in different regions of the spectrum. As a consequence, we can read the data by shining laser beams on the molecules and noting the wavelengths that do not pass through to the detector. Because we can alter the structure of bacteriorhodopsin with one laser and then, with another laser, determine which intermediates have formed, we have the needed basis for writing to and then reading from memory.

Most devices under study make use of the resting state and one intermediate of bacteriorhodopsin. One state is designated as 0 and the other as 1, and switching between the states is controlled by a laser beam. Many early memory devices based on bacteriorhodopsin could operate only at the extremely cold temperature of liquid nitrogen, at which the light-induced switching between the initial *bR* structure and an intermediate known as the *K* state could be controlled. These devices were very fast compared with semiconductor switches (the *bR* to *K* conversion takes place in a few trillionths of a second, compared with the few billionths of a second that common semiconductor devices require). But the need for such low temperatures precluded general application.

Today most bacteriorhodopsin-based devices function at or near room temperature, a condition under which another intermediate, *M,* is stable. Although most bacteriorhodopsin-based memory devices incorporate the *bR*-to-*M* switch, other structures may actually prove more useful in protein-based computer systems.

Parallel Processing

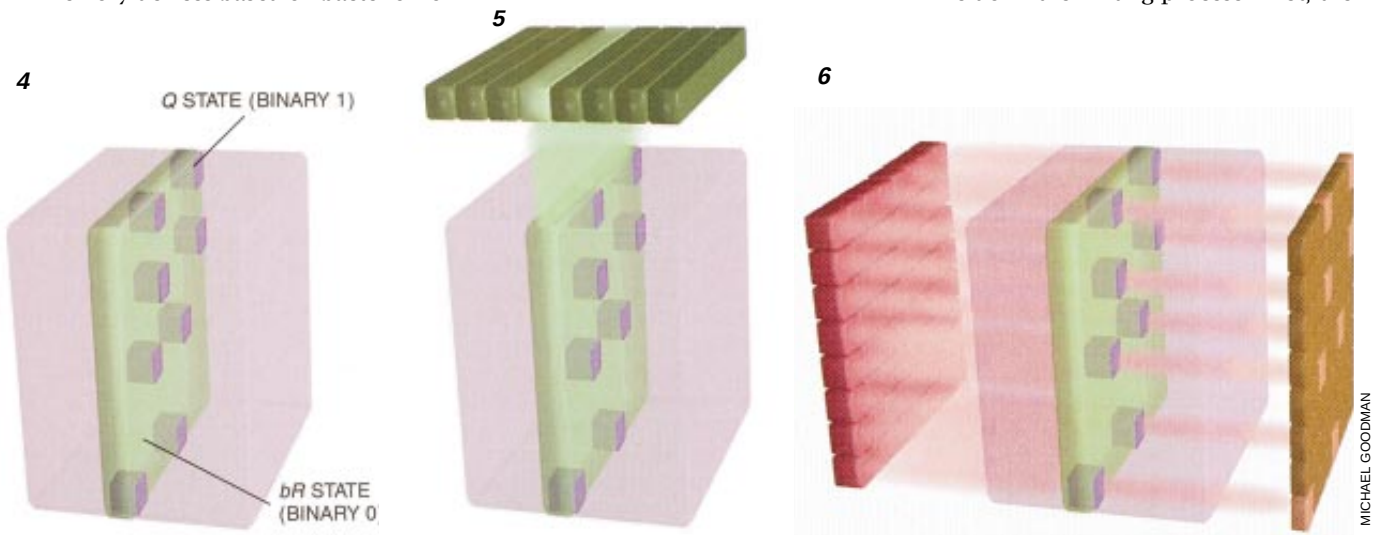
Certain of the intermediates produced after bacteriorhodopsin is initially exposed to light will change to unusual structures when they absorb energy from a second laser beam, in a process known as a sequential one-photon architecture. For example, such a branching reaction occurs from the *O* intermediate to form *P* and *Q*. These structures are generated by two consecutive pulses of laser light—first green light, then red. Although *P* is fairly short-lived, it relaxes into a form known as *Q,* which is stable for extended periods, even up to several years. Because of its extended stability, the *Q* state has great significance in the search for long-term, high-density memory.

The intermediates *P* and *Q,* formed in the sequential one-photon process, are particularly useful for parallel processing. For writing data in parallel, our approach incorporates another innovation: three-dimensional data storage. A cube of bacteriorhodopsin is surrounded by two arrays of laser beams placed 90 degrees from each other. One array of lasers, all set to green and called paging beams, activates the photocycle of the protein in any selected square plane, or page, within the cube. After a few milliseconds, when the number of *O* intermediates reaches near maximum, the other laser array—this time of red beams—is fired.

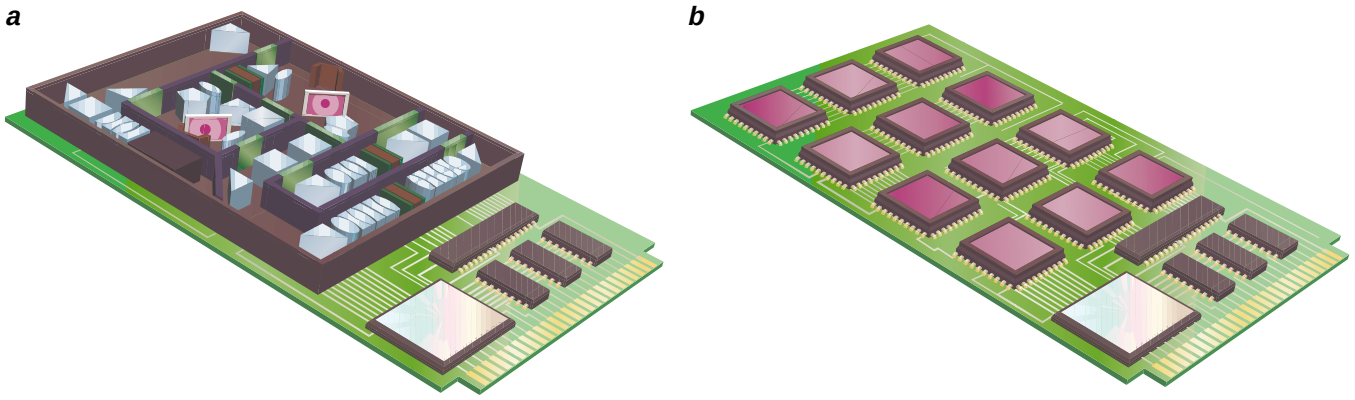
This second array is programmed to illuminate only the region of the activated square where data bits are to be written, switching the molecules there to the *P* structure. The *P* intermediate then relaxes its structure to form the highly stable *Q* state. If we assign the *bR* structure to binary state 0 and both *P* and *Q* to binary state 1, the process is analogous to the binary switching that takes place in semiconductor or magnetic memory. Because the laser array can activate molecules in various places throughout the chosen illuminated page, multiple data locations, known as addresses, can be written to simultaneously—in other words, in parallel.

Our system for reading stored memory—whether during processing or during the extraction of a result—relies on the selective absorption of red light by the *O* intermediate. To read multiple bits of data in parallel, we start just as we do in the writing process. First, the

READING DATA



then relax to the *Q* structure (*4*). Reading from the protein-based memory is begun by again activating the plane with green light (*5*). Then, red lasers of low intensity are fired. Molecules that were originally in the *bR* state absorb the red light, and molecules in the *P* or *Q* state allow the low light levels to pass through. Hence, the resulting pattern of dark and light—that is, 0's and 1's—can be picked up by a detector placed directly opposite from the red laser array (*6*).



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COMPUTERS OF THE FUTURE might be hybrids, consisting of cards with both proteins (*purple*) and semiconductors. The cards shown here, which have not yet been built, could provide associative memory (*a*) and three-dimensional memo-

green paging beam fires at the square of protein to be read, starting the normal photocycle of the molecules in the *bR* state. After two milliseconds, the entire laser array is turned on at a very low intensity of red light. The molecules that are in the binary 1 state (*P* or *Q* intermediates) do not absorb these red beams or change their state.

But the molecules that started out in the original binary 0 state (*bR*) do absorb the beams (but do not change their structure), because they have cycled to the red-absorbing *O* intermediate. A detector images the light passing through the cube of memory and records the location of *O* and of *P* or *Q* structures—or in terms of binary code, the detector reads 0's and 1's. The process is complete in approximately 10 milliseconds, a rate of 10 megabytes per second for each page of memory.

Three-Dimensional Memories

In addition to facilitating parallel processing, three-dimensional cubes of bacteriorhodopsin provide much more memory space than do two-dimensional optical memories. For example, a relatively recent, nonbiological memory system incorporates a thin film of magnetic material that is written on by a laser beam and erased by a magnetic field. These memories are two-dimensional because data are stored on the surface of the disk. Such two-dimensional memories have a storage capacity that is limited to about 100 million bits per square centimeter.

In contrast, three-dimensional optical memories can theoretically approach storage densities of one trillion bits per cubic centimeter. In practice, optical and hardware limitations lower possible densities for volumetric memories. Nevertheless, most investigators believe a 300-fold improvement in storage capacity over two-dimensional devices should be possible. Indeed, I anticipate that the major near-term impact of bioelectronics on computer hardware will be in the area of volumetric memory.

Speed is also an important benefit of volumetric memories. The combination of three-dimensional storage with the use of parallel architectures enhances the speed of such memories, just as parallel processing in the human brain overcomes relatively slow neural processes and allows the brain to be a thinking machine with fast reflexes and rapid decision-making capability. The entire writing process described above takes place in about 10 milliseconds. If we illuminate a square measuring 1,024 bits by 1,024 bits within a larger cube of protein, we can write 1,048,576 bits of data, or about 105 kilobytes, into memory in a 10-millisecond cycle. These values represent an overall write speed of 10 million characters per second, comparable to slow semiconductor memory. Yet each memory device can access more than one data cube, and the speed of the memory is proportional to the number of cubes operating in parallel. Thus, an eight-cube memory would operate much faster, at 80 million characters per second.

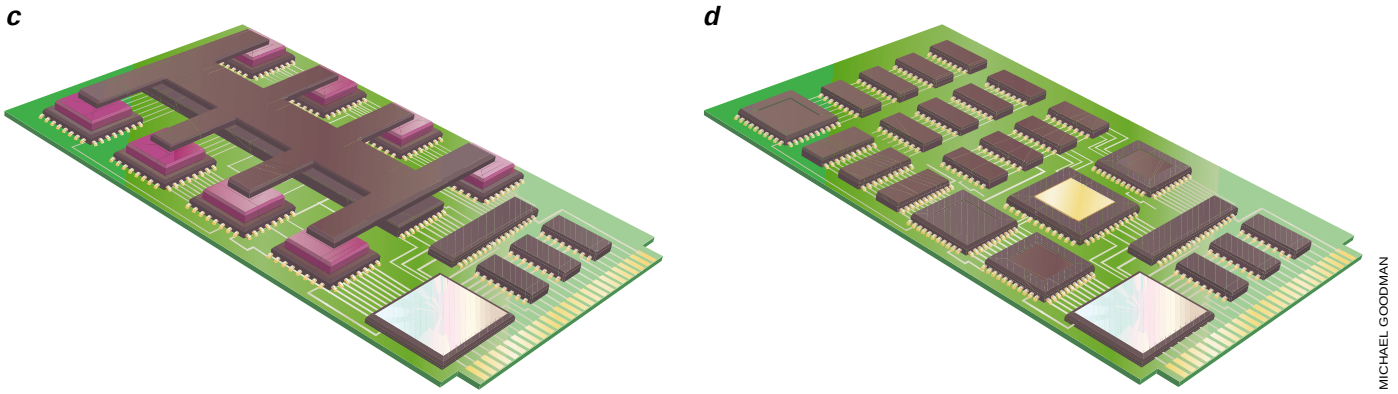
Cubes of memory must be extremely uniform in their composition to ensure accurate reading and writing, because too many or too few molecules in one region will distort information stored there. Manufacturing the cubes in low gravity can produce the needed homogeneity for memory devices. Two space shuttle flights investigating this possibility were sponsored by the W. M. Keck Center for Molecular Electronics at Syracuse University in collaboration with BioServe Space Technologies, the U.S. Air Force Rome Laboratory and the National Aeronautics and Space Administration. The results have been encouraging, and more flights are planned.

Several other types of computer systems based on bacteriorhodopsin are being investigated. For example, biological molecules seem to hold promise as components of the associative memories needed for neural networks and, eventually, for artificial intelligence.

Neural Networks

Associative memories operate rather differently from the memories that dominate current computer architectures. This type of architecture takes a set of data, often in the form of an image, and scans the entire memory bank until it finds a data set that matches it. In some cases, the computer will find the closest match if it cannot find a perfect match, in a sense taking an educated guess at an answer. Because the human brain operates in a neural, associative mode, many computer scientists believe large-capacity associative memories will be required if we are to achieve artificial intelligence.

My laboratory has developed an associative-memory device that relies on the holographic properties of thin films of bacteriorhodopsin. Holograms allow multiple images to be stored in the same segment of memory, permitting large data sets to be analyzed simultaneously. The memory system is based on the classic design of Eung G. Paek and Demetri Psaltis of the California Institute of Technology [see "Optical Neural Computers," by Yaser S. Abu-Mostafa and Demetri Psaltis; SCIENTIFIC AMERICAN, March 1987]. We find that bacteriorhodopsin offers distinct advantages over the photorefractive crystals used to fabricate these memories. Because the protein is more sensitive to light than are inorganic crystals, lower light levels can be employed. In consequence, less energy is needed for writing to and reading from memory, and the speed of these processes improves. Further, bacteriorhodopsin can be written to and read



ry—32 gigabytes of permanent memory (*b*) and eight gigabytes of removable memory (*c*). When combined with a semiconductor central processing unit (*d*), these cards form a complete computer system with enhanced capabilities.

from many more times than can crystals, which suffer from fatigue after repeated read-write cycles.

As studies of natural bacteriorhodopsin continue, many laboratories are also exploring the value of modified forms of the protein in computer devices. Specifically, they are studying genetically engineered versions of the protein, in which one amino acid replaces another in order to enhance the properties needed for particular applications. For example, the lifetime of the *M* state in the photocycle can be lengthened by removal of an internal amino acid from the protein, as shown by Norbert Hampp and Christoph Bräuchle of the University of Munich, in collaboration with Oesterhelt.

Of course, biomolecular computers represent the ultimate goal. As I mentioned earlier, however, most scientists believe the first step in the development of protein-based computers will be the generation of hybrid systems that combine the best features of semiconductor and molecular architectures. In particular, hybrid technology, composed in part of high-density, protein-based memory, may help solve the lingering problem of memory capacity.

During the past decade, the speed of computer processors increased almost 1,000 times, whereas external data storage capacities increased by only a factor of 50. Also, the transfer of data within the computer remains the principal bottleneck that limits performance. Parallel processing and light-based interconnections, both made faster with hybrid computers that exploit the efficient switching of biological molecules, allow for the storage, transfer and manipulation of massive amounts of data.

To explore the possible value of hybrid computers, my laboratory is currently designing one that contains four types of memory units or processors, known as cards. The card with the central processing unit of this computer will consist of traditional semiconductor technology. Two cards will contain protein-based volumetric memory with a total capacity of roughly 40 gigabytes. One of these cards will be a fast, permanent, random-access memory using no moving parts; the other will offer less expensive, removable, long-term data storage. The fourth card will contain an associative memory based on films of bacteriorhodopsin.

The Future of Computers

The hybrid computer we envision would be highly flexible. By taking advantage of particular combinations of the memory cards described above, the computer should be able to handle large pools of data, carry out complex scientific simulations or serve as a unique platform for investigations of artificial intelligence. With close to a terabyte (10^{12} bytes) of memory in cubes of bacteriorhodopsin, this machine would handle large databases with alacrity. Associative memory processing coupled with volumetric memory would make database searches many orders of magnitude faster than is currently possible. Because this hybrid computer can be designed to function as a neural associative computer capable of learning and of analyzing data and images in much the same way as the human brain, the likely importance of hybrid computers to studies in artificial intelligence cannot be underestimated.

Although my group and others have had remarkable success developing volumetric memories and associative processors, more work is needed before a fully operational hybrid computer can be built. Along the way toward developing a powerful yet reasonably priced design, other competing architectures may replace many of the hardware components we have described. Nevertheless, we are confident that hybrid computers of some type will be available within the next eight years.

We further expect that during the next two decades, they will evolve into the dominant architectures for certain types of computing, such as for scientific calculations and multimedia applications. Personal computer users will benefit by having large and inexpensive memory boards that have many gigabytes of data storage and removable memory components that contain a few gigabytes of data storage in a small cube. Imagine the advantage of carrying in your pocket a small cube storing the equivalent of a comprehensive encyclopedia and all the words you have written in the past 10 years.

But the most dramatic application may well be found in yet another realm. With terabytes of data storage, neural associative capabilities and a high capacity for parallel processing, hybrid computers will, for the first time, incorporate the three crucial hardware requirements for artificial intelligence. We are indeed at the threshold of an exciting new era in computing.

FURTHER READING

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