Bioelectronics and Protein-based Devices
Robert R. Birge

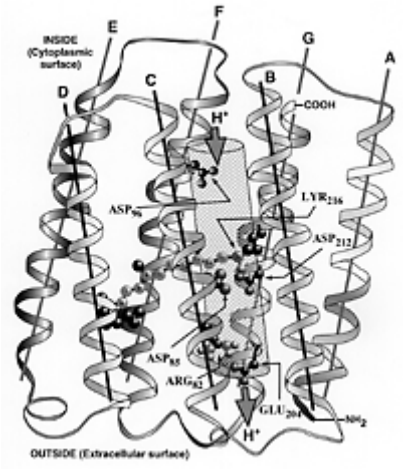

Fig. 1 A schematic picture of bacteriorhodopsin

Molecules form the basis of life, and when combined to form biological organisms, yield highly sophisticated systems which perceive, manipulate, self-repair, think, calculate and feel. Although digital computers can carry out calculations with a speed and precision far superior to humans, in the other five areas, even simple biological systems are superior. In short, biology has achieved through billions of years of evolution, complex systems that have unique attributes that have to date escaped duplication within the realm of semiconductor and software systems.

Chess enthusiasts were recently surprised and perhaps dismayed to watch IBM's Deep Blue computer beat the world's leading [human] chess master, Garry Kasporov [for details see www.chess.ibm.com/home/html/ b.html]. It now seems clear that a computer will soon be able routinely to beat the best human chess masters. Such an accomplishment should not be regarded as an example of artificial intelligence. Chess is a game, and follows well-defined rules. Such constraints permit programmers to test all possible moves, and make decisions based on rule-based logic. While the hardware and software responsible for Deep Blue's accomplishments are very impressive, they do not combine to yield artificial intelligence.

Thus nature still retains the edge over human engineering in many aspects of global computational/intellectual endeavors. Many scientists, and most humanists, will argue that human engineering will never achieve the level of creation and creativity that is evidenced by the human brain, and nature in general. Many scientists and engineers, however, believe that given enough CPU power, memory and data bandwidth, there is no limit as to what can be accomplished. We make no attempt here to arbitrate between these two conflicting views of evolutionary versus human engineering. Rather, we suggest that if our goal is to compete with nature, we need to learn as many of its secrets and make use of its materials and methods to the extent possible.

During the past two decades, my research group has been exploring the potential use of biological systems in computer architectures. Our approach is often called biomimetic, in that we try and use native and genetically engineered proteins in architectures that are often designed to mimic the way nature does things. We seek to make both associative memories, that mimic the data storage and retrieval capabilities of the human brain, and volumetric

memories, that can store both image and digital data within three-dimensional solids of a protein matrix. Working prototypes are now in the second generation, but much remains to be accomplished before commercial systems will be available. Here, we give a brief outline of how our devices work and a progress report. We will also explore what impact such systems may ultimately have on computer artists.

Interest in exploring the computer applications of bioelectronics dates back to the early 1970s and the discovery by Walther Stoekenius and Dieter Oesterhelt at Rockefeller University, New York, of a bacterial protein that has unique photophysical properties. The protein is called bacteriorhodopsin and it is grown by a salt-loving bacterium that populates salt marshes. In the native organism, this photosynthetic protein allows the bacterium to grow when the concentration of oxygen is insufficient to sustain respiration. Upon the absorption of light, the protein pumps a proton across the membrane and drives the synthesis of ATP. The name bacteriorhodopsin derives from its photochemical similarities to rhodopsin, the visual pigment in the eye. Russian scientists were the first to recognize and explore the potential of this protein in optical computing.

Funded by "Project Rhodopsin", and headed by the late Yuri Ovchinnikov Russian scientists at five laboratories, explored the use of this protein in photochromic and holographic devices. Ovchinnikov was not only a highly respected molecular biologist, but also had the ear of the Soviet military leaders. He convinced them that Soviet science could leap-frog the west in computer technology by exploring bioelectronics and garnered significant funding for his Project. Many of the applications were military and the details of this ambitious project may never be fully known. Informal reports from Russian scientists currently in the U.S. indicate the successful creation of sophisticated optical computing architectures that carried out real-time data transformations. Nevertheless, the unusual photochemical and holographic properties of this protein were published and stimulated the international research effort that continues today.

Bacteriorhodopsin is a membrane bound protein with seven alpha-helical segments that span the membrane. A light absorbing group [called the chromophore] embedded inside the protein matrix converts the light energy into a complex series of molecular events that pump the proton. Scientists using the protein for bioelectronic devices exploit the fact that this complex series of thermal reactions results in dramatic changes in the optical and electronic properties of the protein [Fig. 2].

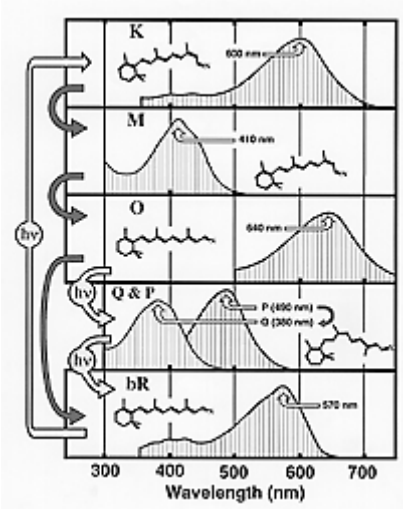

Fig. 2 Absorption spectra and conversions of the protein intermediates

The excellent holographic properties of the protein derive from the large change in refractive index that occurs following light activation. Furthermore, bacteriorhodopsin converts light into a refractive index change with remarkable efficiency [approximately 65%]. The size of the protein is ten times smaller than the wavelength of light which means that the resolution of the thin film is determined by the diffraction limit of the optical geometry rather than the "graininess" of the film. [The Soviet military exploited this property by making thin films of bacteriorhodopsin, called Biochrome, for use as microfiche recording materials.] Also, the protein can absorb two photons simultaneously with an efficiency that far exceeds other materials. This latter capability allows the use of the protein to store information in three dimensions [see below]. In addition, the protein gives off an electrical signal that changes polarity as a function of its current conformation, or state. This latter characteristic can be used to design memories that use light to write the information and electronics to monitor the data. Finally, the protein was designed by nature to function under conditions of high temperature and intense light, a necessary requirement for a salt marsh bacterial protein.

When the protein absorbs light, it undergoes a complex photocycle which generates intermediates with absorption maxima spanning the entire visible region of the spectrum [Fig. 2]. Many of the early optical devices and memories based on bacteriorhodopsin operated at liquid nitrogen temperature and utilized photochemical switching between the bR and K states. While these devices were efficient and potentially very fast [the bR¤K interconversions take place in a few picoseconds], the use of cryogenic temperatures precluded general application. Most current devices operate at ambient or near ambient temperature and utilize the following two states: the initial green — red absorbing state [bR] and the long-lived blue absorbing state [M]. The forward reaction only takes place via light activation and is complete in ~50 ms. In contrast, the reverse reaction can be either light activated or can occur thermally. The light activated M -' bR transition is a direct photochemical transformation.

The thermal M -' bR transition is highly sensitive to temperature, environment, genetic modification and chromophore substitution. This sensitivity is exploited in many optical devices based on bacteriorhodopsin. Another reaction explored here is a photochemical branching reaction from the O intermediate to form P. This intermediate subsequently decays to form Q, a species that is unique in that the chromophore breaks the bond with the protein but is trapped inside the binding site. The Q intermediate is stable for extended periods of time [years] but can be photochemically converted back to bR. This branching reaction has great potential for long term data storage as discussed below.

Associative memories mimic the way the human brain stores and retrieves information.

We now describe some of the unique optical memories and processors that are being made by using bacteriorhodopsin. The first device is a Fourier transform associative memory/ processor. Associative memories operate in a fashion quite different from the serial memories that dominate current computer architectures. These memories take an input data block [or image], and independently of the central processor, "scan" the entire memory for the data block that matches the input. In some implementations [ours], the memory will find the closest match if it cannot find a perfect match. Finally, the memory will return the data block in memory that satisfies the matching criteria or it will return the address of the data block to permit access of contiguous data. Some memories will simply return a binary bit indicating whether the input data is present or not present. Because the human brain operates in a neural,

associative mode, many computer scientists believe that the implementation of large capacity associative memories will be required if we are to achieve genuine artificial intelligence.

Thin films of bacteriorhodopsin are the photoactive components in the Fourier transform holographic [FTH] associative memory shown in Fig. 3. The actual operation of this memory is rather complicated and the interested reader is directed to the additional reading material at the end of this paper for more detailed discussion. Our interest here is to explain what a memory like this can do, and the potential relevance of such a memory to artificial intelligence and the digital arts. Let us start with a simple demonstration based on the diagram shown in Fig. 3.

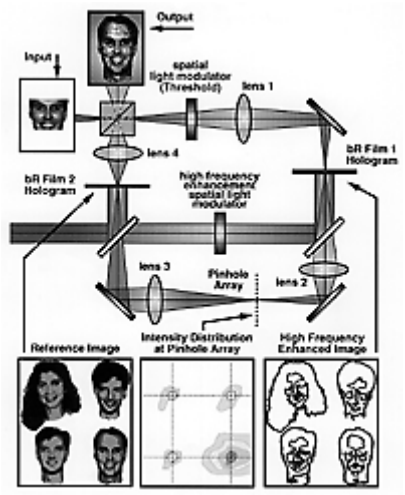

Fig. 3 Schematic diagram of the Fourier transform holographic associative memory

Reference data [e.g., the four faces shown at lower left] are stored in the memory as holographic Fourier images on the protein thin films. We now introduce an input image that we want to "associate" with our reference data, in this case a portion of one of the faces. By a process known as Fourier transform holographic association, this image "interacts" with all the images simultaneously, and selectively illuminates the pinhole that spatially corresponds with the image that is the closest match to the input image [or portion thereof]. The output of the memory is the full image within the stored data base that represents the best match to the input.

This might seem to be a lot of work for little reward, but the process, and the hardware that makes it possible, have real-world applications. First, one can store thousands of images simultaneously, and select the best match from this set in a matter of nanoseconds [the time it takes light to travel about ten feet]. The speed is typical of all optical parallel computing processes. If no match is found, a new set of images can be read in and the process repeated. Christoph Bräuchle and Norbert Hampp [University of Munich] and Dieter Oesterhelt[Max Planck Institute in Munich] have developed a similar optical system that will select a page of text with the largest occurrences of a given input word, or rapidly select the correct denomination of paper currency. What happens if there are two images that match with identical, or nearly identical, levels? Actually, this happens all the time, and the memory is designed to display the top five or ten images in sequence, for further analysis.

The applications to artificial intelligence are numerous, because one can fill the data base with mixtures of images and words, and associate in both realms simultaneously. Some believe that

creativity with humans can best be described in terms of association within a broad data base of experience, and that discovery is a process of association across the nominal boundaries that confine our perception based on prior learning and societal constraints.

Our current interest is to miniaturize the optics onto a single PCI computer card so that data, both image and text, can be manipulated and associated in a digital environment. An internal laser will drive the circuit, and data will be loaded via an internal spatial light modulator. If this project succeeds, we will have an associative memory that can be inserted into standard computers. This card can also be used to scan large data bases containing graphic images and select an image that is closest to the input image.

To more fully appreciate the potential applications of such a memory in the graphic arts, consider a few examples. A quick sketch involving only a few lines could be used to select images with similar content from an extremely large data base in real time. The closest match based on the high-frequency enhanced images is found [note that the high frequency enhanced images are closer to line art, anyway]. A graphic artist could also use such a memory to create new art by drawing rough sketches and allowing the computer to associate the input sketches with a data base of abstract images. The artist could then select from the five or ten most pleasing "associations", and then add the chosen image to the master. Interactive human and computer animation could be enhanced through autoassociative image reconstruction. For example, the person draws a rough image of a person, and the computer fills in the details from a data base of scaled images.

Storing data in three dimensions.

BCO — beam condensing optics
BEO — beam expending optics
CCD — charge coupled device
DBS — dichroic beam splitter
DC — data cuvette, containing the
protein in a transparent
polymer matrix
DCKH — data cuvette, kinematic holder
PTC — Peltier temperature controler
QHL — quarz halogen lamp
SLM — spatial light modulator

The digital arts are notorious for requiring large random access as well as disk memories. A single low resolution image [1024x768x32 bits] requires over three megabytes [MB] and a high resolution image [6000x4800x32 bits], more typical of today's professional artists, requires 115 MB. Less than ten such images require a gigabyte [GB], and thus it is not surprising that the average digital artist requires many GB of fast disk memory and hundreds of GB of removable media. Many scientists believe that the major impact of bioelectronics on computer hardware will be in the area of three-dimensional memory. The advantages of three versus two dimensional memories is in capacity, and in some cases, data access bandwidth. Two dimensional optical memories have a storage capacity that is limited to ~1/(wavelength)^2, which yields approximately 10^8 bits/cm^2. In contrast, three-dimensional memories can approach storage densities of 1/(wavelength)^3, which yields densities of approximately 10^12 bits/cm^3. In principle, an optical three-dimensional memory can store roughly three orders of magnitude more information in the same size enclosure relative to a two-dimensional optical disk memory. In practice, optical limitations and issues of reliability

lower the above ratio to values closer to 300. Nevertheless, a 300-fold improvement in storage capacity is significant. The protein bacteriorhodopsin offers a rather unique approach to three dimensional data storage by exhibiting what is known as a branching reaction. The protein is encapsulated into a polymer which is sealed inside a small plastic cuvette of dimensions 1 cm x 1 cm x 3 cm. By using the methods described below, it is possible to store about ten GB in one such cuvette. What makes this exciting and potentially valuable is not so much the large storage density, but the inexpensive nature of the data storage cuvettes. A single cuvette is made of plastic, inexpensive polymer and a protein can be prepared in large quantities via fermentation.

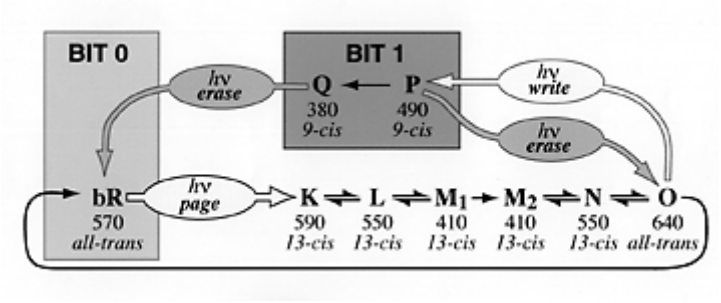

Fig. 5
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We discussed above the use of the P and Q states for long-term data storage. The fact that these states can only be generated via a temporally separated pulse sequence provides a convenient method of storing data in three dimensions by using orthogonal laser excitation. The process is based on the sequential scheme (see Fig. 5) where K, L, M, N and O are all intermediates within the main photocycle, and P and Q are intermediates in the branching cycle. The numbers underneath the letters give the wavelengths of the absorption maxima of the intermediates in nanometers [e.g. bR has a maximum absorbance at 570nm, or yellow-green region, O absorbs at 640nm, in the red].

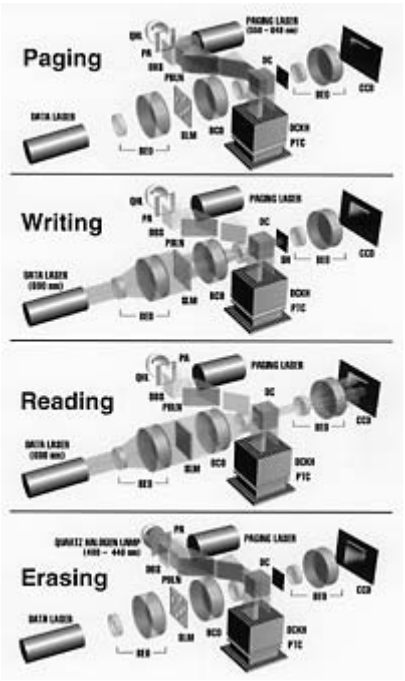

Fig. 4 Schematic diagram of the four operations of the three-dimensional memory

The reading and writing process starts by selecting a very thin region [~15 micron] inside the data cuvette by a process called "paging" [top, Fig. 4]. In this process, the paging lasers [there are two, one on each side of the data cuvette, but only one is shown for clarity] with a wavelength in the region 550—640 nm initiates the photocycle within a ~15 micron slice of the memory medium. The photocycle will return to the resting state [bR] in about 10 ms, the time window during which subsequent writing or reading must takes place. In the absence of secondary laser stimulation, the protein within the paged region will simply return to the resting state.

Data are written in parallel via a branching reaction.

A parallel write is accomplished by using the sequential one-photon optical protocol. The paging beam activates the photocycle of bacteriorhodopsin and after a few milliseconds the O intermediate approaches maximal concentration. The data laser and the LCSLM are now activated [l = 680nm, Dt ‰ 3 ms] to irradiate those volume elements into which 1 bits are to be written. This process converts O to P in these, and only these, locations within the memory cuvette. After many minutes the P state thermally decays to form the Q state [the P -' Q decay time, tP, is highly dependent upon temperature and polymer matrix]. The write process is accomplished in ~10 ms, the time it takes the protein to complete the photocycle.

Data are read in parallel one page at a time.

The read process takes advantage of the fact that light around 680 nm is absorbed by only two intermediates in the photocycle of light-adapted bacteriorhodopsin, the primary photoproduct K and the relatively long-lived O intermediate [see Fig 2]. The read sequence starts out in a fashion identical to that of the write process by activating the 568nm paging beam. After two milliseconds, the data timing [DTS] and the data read [DRS] shutters are opened for 1ms, but the SLM is left off allowing only 0.1% of the total laser power through. A CCD array [clocked to clear all charges prior to reading] images the light passing through the data cuvette. Those elements in binary state 1 [P or Q] do not absorb the 680nm light, but those volumetric elements that started out in the binary 0 state [bR] absorb the 680nm light, because these elements have cycled into the O state. Noting that all of the volumetric elements outside of the paged area are restricted to the bR, P or Q states, the only significant absorption of the beam is associated with O states within the paged region. The CCD detector array therefore observes the differential absorptivity of the paged region, and the paged region alone. This selectivity is the key to the read operation, and it allows a reasonable signal-to-noise ratio even with thick [1—1.6 cm] memory media containing >103 pages. Because the absorptivity of the O state within the paged region is more than 1000 times larger than the absorptivity of the remaining volume elements combined, a very weak beam can be used to generate a large differential signal. The read process is complete in ~10 ms which gives a rate of 10 MB/s. Each read operation must be monitored for each page, and a refresh operation performed after ~1000 reads. While data refresh slows the memory slightly, page caching can minimize the impact.

Data are erased in multiple page sets using incoherent blue light.

A filtered quartz halogen lamp provides blue light to photochemically convert both P and Q back to bR. Because this light is not coherent, single page focusing is not possible, and multiple pages are cleared simultaneously. The optimal wavelength for erasing data is ~410

nm. Alternatively, one can clear an entire data cuvette by using incoherent light in the 360—450 nm range. The latter option may prove useful for some less expensive implementations.

In closing, I need to emphasize that more work is necessary before the associative memory or the three-dimensional memory will be available to the average user. But the reader can rest assured that both types of memory will be manufactured in some format during the next decade. Nature has much to teach us as regards the manipulation and storage of information, and the tools for exploring nature, and modifying natural materials, are becoming increasingly useful and powerful. The future of biomimetic engineering should provide both excitement for the researcher and utility for the electronic artist.

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