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Bacteriorhodopsin as a nanomemory

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ABSTRACT

Bacteriorhodopsin (BR) is produced by halobacteria and is the key protein of their photosynthetic capabilities. Rather soon after its discovery, the first proposals for technical applications of this protein were brought up. Various technical and in particular optical applications of BR have been explored since that time in several research groups. In this paper, the area of photochromic applications of BR is reviewed. BR is so attractive over other proteins and conventional inorganic or organic photochromic materials. BR not only is an attractive candidate to be the first photochromic biomolecule in a technical application but also allow exploration of strategies how biomaterials with technically interesting physical functions can be used as components in technical devices.

Keywords: protein memory, bacteriorhodopsin, photocycle.

INTRODUCTION

An extrapolation of Moore's law [10] suggests that semiconductor feature sizes will reach the molecular domain by 2030. The existing lithographic techniques are struggling to create nanoscale devices as the feature sizes shrink below the wavelength of the light. On the other hand, molecular electronics [69] is getting mature in fabricating faster nanoscale devices. The key advantage of molecular electronics is its ability to fabricate nanoscale devices in a "bottom-up" fashion in contrast to the "top-down" approach adopted by lithographic techniques. Bioelectronics can be considered as a subdomain of molecular electronics that investigates the adoption of biological molecules (proteins, chromophores, etc.) in fabrication of nanoscale electronic or photonic devices. Although several proteins have been explored for use in nanoscale devices, bacteriorhodopsin (BR) has received wide attention. The BR protein has all the desired properties for usage in both volumetric (3-D) memory and associative memory applications [1].

Bioelectronics is a subfield of molecular electronics that investigates the use of native as well as modified biological molecules (chromophores, proteins, etc.) in electronic or photonic devices. Because evolution has often solved problems of a nature similar to those that must be solved in harnessing organic compounds and because self-assembly and genetic engineering provide sophisticated control and manipulation of large molecules or ensembles, bioelectronics has shown considerable promise. Much of the current research effort in bioelectronics is directed toward self-assembled monolayers and thin films, biosensors, and protein-based photonic devices. Although a number of proteins have been explored for device applications [28-32], bacteriorhodopsin has received the most attention. Russian scientists, under the leadership of the late Yuri Ovchinnikov, were the first to recognize and explore the potential of bacteriorhodopsin. Ovchinnikov was not only a highly respected molecular biologist and director of the Shemyakin Institute but also a forceful advocate of bioelectronics within the decision-making apparatus of the former Soviet Union. He proposed that Soviet science could leapfrog the West in computer technology by exploring bioelectronics and garnered significant funding to explore this possibility under what became known as "Project Rhodopsin". Many of the applications were military and the details are obscure (i.e., remain classified). Nevertheless, the photochromic and holographic properties of this protein were published and stimulated an international research effort that continues today. One of the best-known accomplishments of this

project was the development of Biochrome, a real-time photochromic and holographic film based on chemically modified polymer films containing bacteriorhodopsin [33], [34]. The principal investigator of this project, Nikolai Vsevolodov, has since moved to the U.S. and serves as the principal scientist of Starzent, a small start-up company that seeks to manufacture high-density holographic memories. Vsevolodov's recent book provides an excellent introduction to the field of protein-based devices [28], [5].

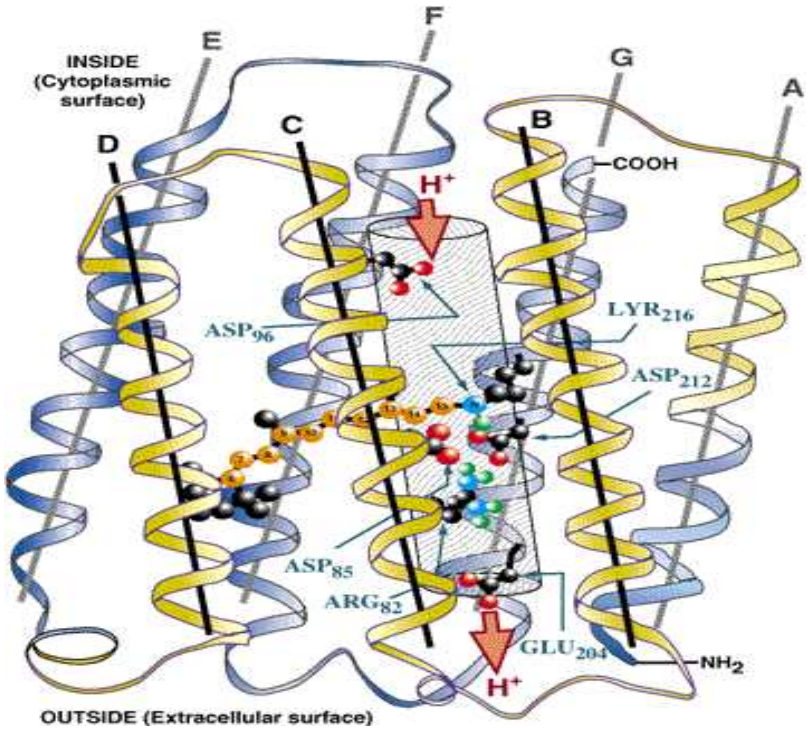

Fig. 1. Bacteriorhodopsin is a membrane-bound protein with seven alpha-helical segments

When it absorbs light, it pumps a proton, which the bacterium uses as a source of energy. We use the protein to store information by using light to induce a change in the geometry of the chromophore (orange atoms). The overall dimcnsions are roughly 40 Angstroms x 40 Angstroms x 50 Angstroms, making it a nanoscale data storage device.

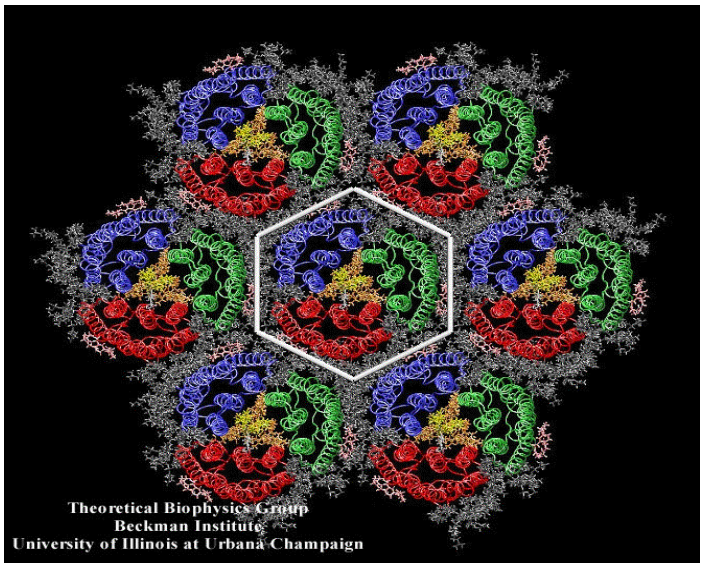

Fig. 2. Structure of the BR molecule

An image about its trimer, crystal-like structure is also should be appreciated.

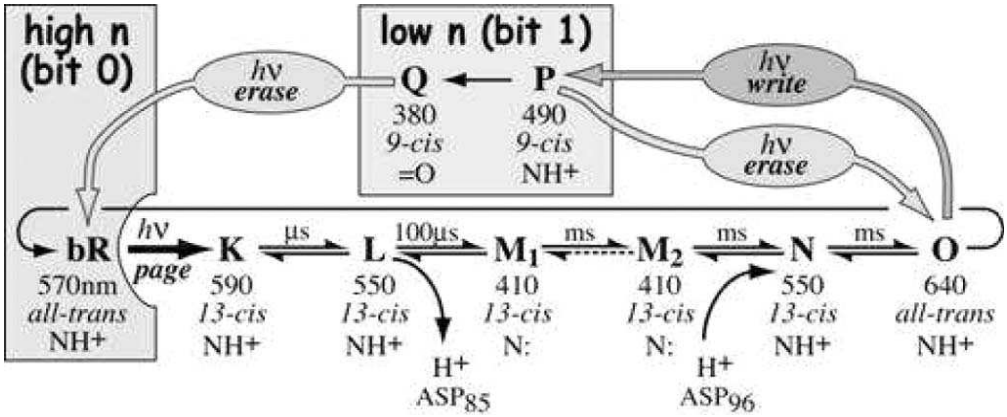

Fig. 3. Branched photocycle of BR.

Bacteriorhodopsin (BR) is grown in the purple membrane of a salt marsh bacterium called Halobacterium salinarium (Fig. 1) [35-39]. When we consider the nature of a salt marsh and the fact that this protein is designed for photosynthetic light energy transduction, we should not be surprised that a microorganism has created, albeit unwittingly, a material with comparative advantages in photonic devices. The protein must operate at high temperatures, under high light fluxes, for extended periods of time for the organism to survive. Furthermore, the protein must function under the chemical stress imposed by a pH gradient that the protein itself creates. What is surprising, however, is the broad range of applications for which this protein shows comparative advantage. These include random access thin film memories [40], [41], [42], neural-type logic gates, photon counters [43] and photovoltaic converters [44], [45], [46], reversible holographic media[47], [48], artificial retinas [49], [50], [51], picosecond photodetectors [52], [53], spatial light modulators [31], [54], [55], associative memories [31], two-photon volumetric memories [54], [56], holographic correlators [57], nonlinear optical filters [58], dynamic time-average interferometers [59], optical limiters [55], pattern recognition systems [60], real-time holographic imaging systems [61], multilevel logic gates [62], optical computing [63], and branched- photocycle volumetric memories [64], [65], [66], [67], [5].

2. Biological function and structure of bacteriorhodopsin

The most extensively studied biological material for creating an artificial photodetector is bacteriorhodopsin (bR), a light sensitive receptor used for signal transduction in Halobacterium salinarium [12], [9], [17]. It exhibits similar structure and photophysical processes to those of rhodopsin found in the eyes of higher order creatures. The bR molecule employs solar energy to transport hydrogen ions across the bacterial cell membrane, thus generating a potential difference necessary for driving the synthesis of adenosine triphosphate (ATP) from adenosine diphosphate (ADP). Under anaerobic conditions the cell membrane grows purple membrane (PM) patches in the form of a hexagonal two-dimensional crystalline lattice of bR trimers (Fig. 2) [13]. Each bR molecule consists of 248 amino acid residues in a polypeptide chain, which is arranged in seven α-helices [5] and encloses the retinal residue, several key amino-acid residues and water molecules within the cavity (Fig. 1) [14]. This cavity defines the proton transport pathway and shields the chromophoric group from external environmental influences. The amino acids surrounding the retinal influence the absorption properties. The crystalline structure is the root of bR's chemical and thermal stability. PM is stable against sunlight exposure in the presence of oxygen for several years. In water, its stability holds for temperatures over 80 C, pH values ranging from 0 to 12 and in the presence of high ionic concentrations (up to 3 M NaCl) [15]. The PM even preserves its colour and photochemical activity in dry conditions, and can withstand temperatures up to 140 C [16], [11].

3. Photocycle of BR as the key to enable information storage

When BR absorbs a photon of light, it passes through a cycle of structural changes, that is, the photocycle of BR [19], [20]. The key result of the changes is the isomerization from all-trans to 13-cis of the retinal chromophore bound at Lys-216 [21]. Each change in the molecular structure is referred to as an intermediate. Fig. 4 shows the intermediates in the photocycle of BR at room temperature. The intermediates are identified with capital letters, and the numbers in parentheses indicate the wavelengths (in nanometers) of the absorption maxima. The thin black arrows indicate the transitions (between the respective intermediates) through thermal fluctuations, whereas the thick colored arrows reflect the photochemically induced transitions. The color of each thick arrow represents the color of the excitation frequency. Naturally, these conformational lightinduced changes are also temperaturedependent, implying that an intermediate can be stabilized ("frozen") at a certain temperature, usually below −10°C (specific to each intermediate). At temperatures below the freezing temperature, the transition to the next intermediate becomes suppressed. The characteristic relaxation times (lifetimes) of some of the intermediates at room temperature are shown next to the respective thin arrows. The photocycle with intermediates can be treated as

a state diagram with intermediates presented as states. Each intermediate has its own absorption spectrum, and thus, intermediates (states) can be optically distinguished from each other. The characteristic absorption spectra of some of the key intermediates (in information-storage-related applications) of BR at room temperature are shown in Fig. 5. The following key properties of the photocycle of BR should be highlighted with regard to information-storagerelated applications [18]:

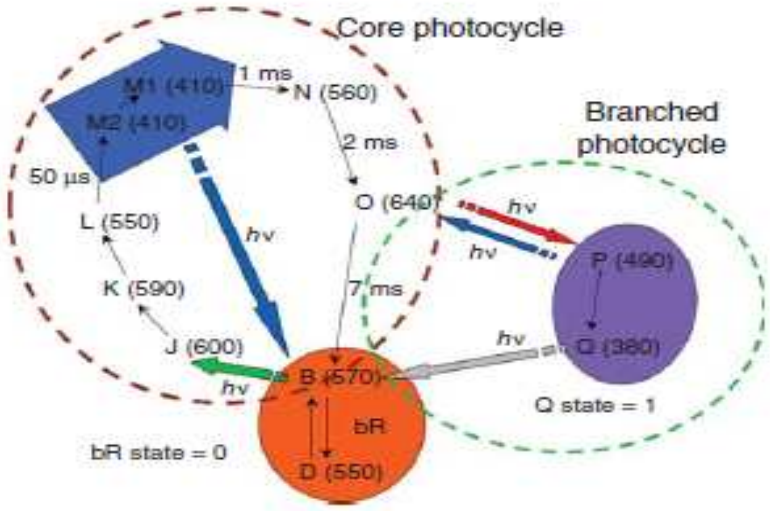

Fig. 4. Schematic of the photocycle of BR at room temperature. bR is the ground state, and the intermediates (states) are identified with capital letters. The numbers in parentheses indicate the wavelengths (in nanometers) of the absorption maxima. The thin black arrows indicate the transitions (between the respective states) through thermal fluctuations, whereas the thick colored arrows reflect the photochemically induced transitions. The color of each arrow represents the color of the excitation frequency.

■ The photocycle of BR consists of several branches [22]. The two most significant (for information-related applications) branches are the core and branched photocycles. During its normal function, the BR molecule remains in the core photocycle. The intermediates in the branched photocycle are not populated at physiological conditions [23]. As described in a following point, for the molecule to go into the branched photocycle, the protein should be exposed to a certain sequence of light [18].

■ In general, the ground state of BR, or the bR state, consists of a 6:4 mixture of the D and B intermediates. Upon exposure to light, all of the protein molecules transition into the B intermediate. From there, they transition into the core photocycle, as illustrated in Fig. 4 [18].

■ In the core photocycle, every transition between any two adjacent intermediates is reversible, with the exception of the transition from M2 to M1. The transition from M2 to M1 is responsible for the irreversible proton transport during the photocycle (deprotonation and reprotonation) [24]. It should be noted that the M2 and M1 intermediates have practically indistinguishable absorption spectra. Consequently, the combination of M2 and M1 is often referred to as the M state [18].

■ The core photocycle could be used for dynamic short-term (volatile) memory applications, such as random-access memory and devices for fast nondestructive optical processing [25]. In this case, the ground state (bR) and the complex M state are usually used as the two binary states, that is, “0” and “1,” respectively. The life- time of the M state at room temperature varies from approximately 1 s for the wild-type BR to a few minutes for certain variants of BR, such as D96N. The wild-type BR is the original form found in nature, whereas variants are genetically engineered mutants of BR. Today, both types, the wild-type BR and BR variants, are commercially available [26]. Furthermore, as mentioned in the Introduction, with the modern advances of genetic engineering, it is very likely that the lifetime of the M state could be further optimized to fit specific applications. However, because the lifetime of the M state is still relatively short, the core photocycle cannot yet be used for nonvolatile memory applications[18].

■ It is the branched photocycle that is being considered for most long-term nonvolatile memory applications. Nature itself manufactured a device with a photocycle that is almost ideally suited for longterm information-storage applications [27]. In this case, the two binary states (i.e., 0 and 1) are represented by the ground state (bR) and either the P or Q intermediate in the branched cycle. The branched photocycle originates at the O intermediate, that is, after deprotonation has taken place. When the protein is illuminated by red light, it branches off from O to P. Then, the protein thermally converts from P to Q. The Q intermediate is isolated from the core photocycle by a relatively large energy gap, which underlies the nonvolatile memory application of BR. To transition from the Q intermediate

back to the bR state in the core photocycle, the protein is exposed to blue light. The process results in the reisomerization of the chromophore to the all-trans configuration and the return of the protein to the ground (bR) state. As illustrated in Fig.5, the bR state and the Q intermediate have quite different absorption spectra and, thus, can be optically distinguished [18].

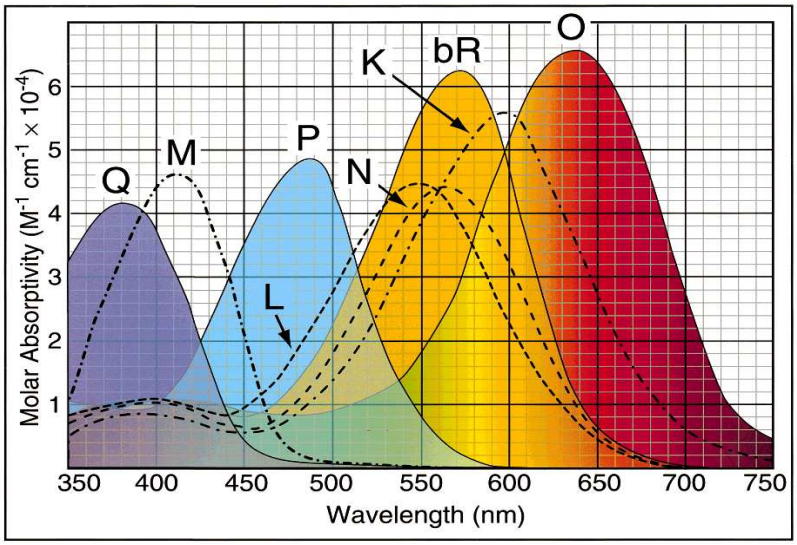

Fig. 5. Schematic illustrating typical absorption spectra of the five key states, bR, M, O, P, and Q, in the photocycle of BR.

4. Data are written in parallel via a branching reaction

The initial process in both writing and reading is the selection and activation of a thin segment of protein within the volumetric memory medium. This thin activated region is called a page, and the activation process is called paging. The thickness of the page is dependent on the optical arrangement and varies from an rms value of 15 µm (multiple prism system) to 100 µm (simple cylindrical lens). Data are then written by using an orthogonal beam of light that is shifted in time so that it photoactivates the O state (Fig. 3) [5].

The process is explicitly documented on the left-hand side of Fig. 6 for a process that writes three bits within the page. The vertical axis of Fig. 6 charts nominal time relative to the firing of the page addressing (or paging) laser. Two milliseconds following paging, the data laser [71] and the data beam spatial light modulator are activated (λ=680 nm, $\Delta t \approx 3$ 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, voxels within the memory cuvette (A voxel is the volumetric pixel formed in the volume element created by a single write pixel overlap with the active page). After many minutes the P state thermally decays to form the Q state. The write process is accomplished in ~10 ms, the time it takes the protein to complete the photocycle. The combination of a paging and write beam are shown at the top of Fig. 7. Note that these beams are not turned on simultaneously but are shown simultaneously for convenience. The use of a prism system for creating a narrow page beam provides near-diffraction limited performance, but at the expense of complexity. Alternative approaches are under investigation. All designs use paging optics on both sides of the data cuvette to enhance resolution, photocycle conversion, and homogeneity. Only one side of the paging optics is shown in Fig. 7 for convenience. The above description describes the process of writing a single bit per voxel, but methods are available that enhance storage density [5].

5. Data are read in parallel by using differential absorptivity

The read process takes advantage of the fact that light of wavelength around 680 nm is absorbed effectively by only two intermediates in the photocycle of light-adapted bacteriorhodopsin, the primary photoproduct K and the relatively long-lived O intermediate (see Fig. 5). If the light beam is timed properly, the K state can be avoided and only the O state will absorb light. This is the approach that is used to image data within an activated page, as shown on the right-hand-side of Fig. 6. The read sequence starts out in a fashion identical to that of the write process by activating the paging beam. After 2 ms, the data laser and the data SLM are turned on, but at a low constant power (roughly 1% of nominal write intensity). This process images the active page onto the CCD detector.

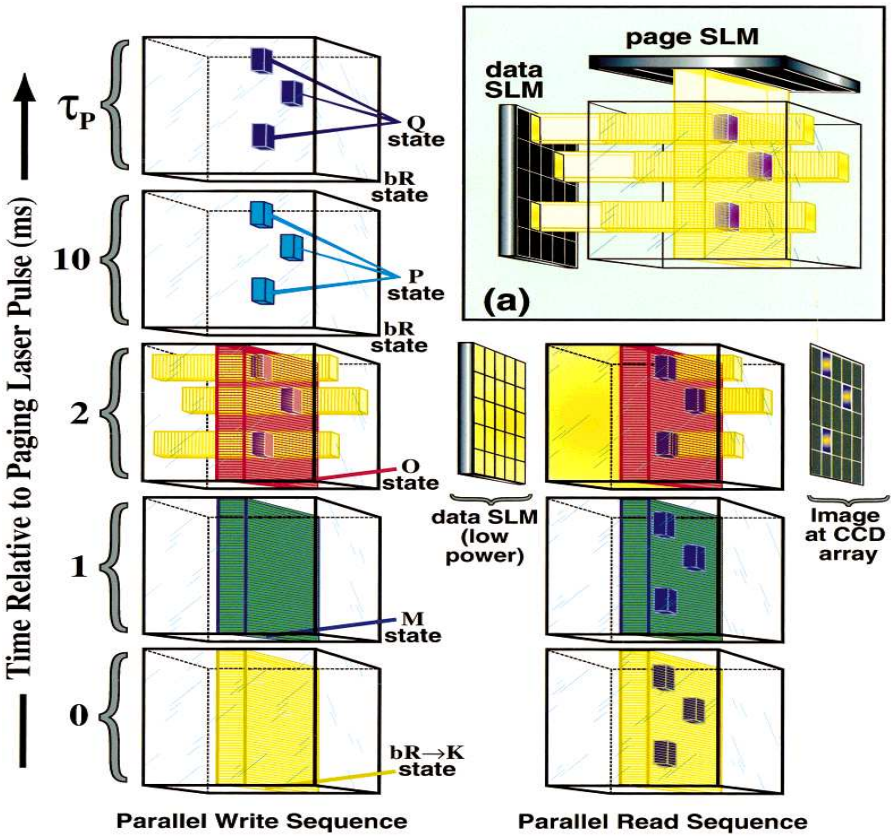

Fig. 6. Parallel write sequence (left) and parallel read sequence (right) for the hypothetical storage and retrieval of three bits of data in a page of memory using the branched-photocycle architecture.

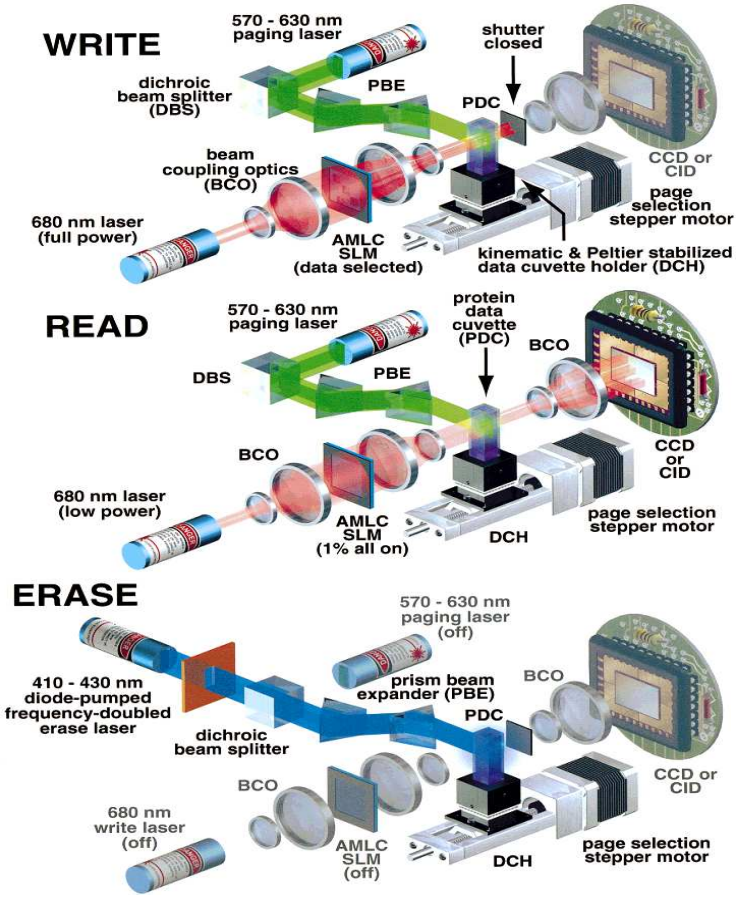

Fig. 7. Read, write, and erase processes based on a level I prototype design.

Those elements in binary state 1 (P or Q) do not absorb the 680 nm light, but those volumetric elements that started out in the binary 0 state (bR) absorb the 680 nm light, because these elements have cycled into the O state (It is purely coincidental that the "O" molecular state is used to monitor the "0" binary 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 about 6 ms, but a second read cannot be carried out until the photocycle has completed thereby limiting multiple read processes to 10 ms cycles. Each read operation must be monitored for each page, and a refresh operation performed after ~1000 reads. The three most recent pages are stored in semiconductor cache memory to minimize the number of refresh operations [5].

6. Data can be erased by page or globally

The P and Q states can both be photoconverted back to bR [68] by using blue light [72] (Fig. 3). If one has access to coherent light, then individual pages can be cleared by using irradiation at or near 410 nm, a wavelength that intercepts both P and Q (Fig. 5). Our early prototypes used the 413 nm output of a kryptonion laser. Such an approach is only useful for level I prototypes, however, and our various level II prototypes are investigating three alternatives. The first is a frequency-doubled diode laser manufactured by NanoLambda Corp., Kerhonken, NY (Fig.7). Other than cost, this approach is adequate and will suffice until blue diode lasers are available. Alternatively, one can clear an entire data cuvette by using incoherent light in the 360-450 nm range. We explore this approach in the prototype described below. A broad-band data clear operation must be carried out in the absence of red light, however, because blue light can activate the photocycle and produce the O state. As one reviewer noted, however, the O state does have appreciable absorptivity in the 360-450 nm range. This situation does not cause a problem, however, because the absence of red light limits the population of O state molecules to the small amount generated by photochemical conversion of P. Because the P and Q states are preferential absorbers of the erase beam, the end photostationary state distribution favors bR by factors of many hundreds, and erasure is efficient. Erasure does not have to be perfect, however, for the memory to work properly. The use of differential absorptivity data read methods allows for an inherent background level of P and Q [5].

7. BR as a holographic storage medium

The excellent holographic properties of the BR protein arise from the fact that the BR protein exhibits a large change in the refractive index when subjected to photo activation. The quantum efficiency of the refractive index is up to 65%. The size of the BR protein is ten times smaller than the wavelength of light. This can help in producing thin holographic mediums [70]. The BR protein has a far superior two photon absorption capability compared to any other material. Apart from all the great holographic properties, as aforementioned, the BR protein can sustain very hot temperatures and intense light. There has been a great deal of research on further improving the BR protein for volumetric data storage. Several genetically engineered versions of the BR protein have already been developed (see, e.g., [5], [6], [7], and [8]). All these excellent properties of the BR protein make it a better choice to build holographic memories than materials such as lithium niobate (LiNbO3) [4], [1].

The usage of BR as the storage medium is based on its highly quantum efficient photocycle. The primary photochemical event in BR involves photoisomerization from all-trans to 13-cis. The photon pumping process of BR is accomplished by the photocycle in Fig. 3. Although there are several states in the photocycle of BR, the states bR (note this is different from the name of the protein BR), M, and Q are of primary interest from the perspective of volumetric data storage. The state bR indicates the resting state of the BR protein. The blue-shifted M and Q states are used in real time [3] and as long-lived [2] holographic memories. The resting state bR indicates a 0-bit and the states M and Q indicate a 1-bit. The M state has a great quantum efficiency and can produce significant changes in the refractive index. Unfortunately, the disadvantage is that the M state is typically very short lived and thus finds application only in real-time storage systems, in contrast to Q. The state Q is highly stable for extended periods of time and thus, can be used in long term data storage. Thus, the two states bR and Q of the photocycle of BR are used to encode 0 and 1 in holographic storage media [1], [70] holographic memories.

CONCLUSION

Using BR instead of conventional chemicals is justified only if there is at least one property which is an exceptional feature for a group of applications, e.g. long-term rewritable optical storage. In principle, BR might be used for this purpose; however, it is difficult to argue why BR is needed for such applications and which advantage BR offers

over conventional materials here. Maybe P and Q states and the electrochromic effects of BR variants are ways to raise the power of BR for long-term storage.

The domain of BR is dynamic applications where hundreds or thousands of cycles between the bR and the M state are required. The excellent reversibility of BR distinguishes this material from conventional ones. Because of the problems with optical recording materials within the last some years, not many of the promising optical techniques received broad attention. The power of computers increased dramatically during the same period. With a new and reliable recording material, the use of optics not only for storage purposes but also for processing should be reconsidered. Among the optical applications of BR, holographic interferometry obviously is the first field of a commercial use of BR.

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