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Biophysics and Quantum Limitation of Photoreceptive Processes

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Definition: This entry paper is an attempt to explain how the discrete nature of light (energy discreteness in the form of photons) constrains the light detection process all along the evolutionary path, in the not-fully-understood photoreceptive systems of unicellular microorganisms (nonimaging systems) and in the complex and well-known visual system of higher organisms (imaging systems). All these systems are perfect examples of the interplay between physics and biology, i.e., they are the perfect topic of research for biophysicists. The paper describes how photoreceptive and visual systems achieve the goal of photon counting, which information is conveyed by a finite number of photons, and which noise factors limit light-detecting processes.

Keywords: rhodopsin; retina; eye; *Euglena gracilis*; noise; information

1. Introduction

It would be difficult to find a more perfect example of the interplay between physics and biology (a perfect topic for biophysical research) than light detection systems along the evolutionary path. Nature had coped with the hard constraint of the quantum nature of light until it came across the wondrous rhodopsin protein, an almost-noise-free photon counter. By means of this passé-partout, nature has succeeded in extracting and handling the maximum amount of information out of a limited amount of photons despite its statistical fluctuation (photon noise) [1].

We could say then that the final goal of a light-detecting system is to capture and count individual photons as nature mastered the art of counting photons as an early evolutionary adaptation. Incorporation of photosensitive proteins in the cell membrane can be traced back to Archaebacteria, such as *Halobacterium halobium*; in this prokaryote, bidimensionally oriented proteins span the cell membrane in almost all its surface, providing cells with a highly efficient photon-capturing device [2]. Successively, three-dimensional (3D) photosensitive structures evolved as light-receptor organelles consisting of a stack of many photosensitive membranes by adapting flagella for the purpose. The unicellular flagellate *Euglena gracilis* is a typical example of these 3D structures; in the apical part of the cell, there is a photoreceptive system composed of an intracellular screen, named eyespot, and a 3D crystalline photoreceptor, named paraflagellar body (PFB), located inside the membrane of the emerging flagellum, whose beating moves the cell into its search for light [3]. According to Eakin, the adaptation of a cilium (basal centriole + microtubular axoneme) as a light detector by the incorporation of a photopigment in its membrane suggests a common ancestry of the taxa bearing light-sensitive cilia [4]. He indicated *Euglena*, with its photoreceptive system, as the very early evolutionary step of the ciliary line leading to the complex vertebrate light sensor.

Photoreceptive and visual systems apparently achieved the goal of detecting (and using) incoming photons. If it was just a matter of detecting and using the energy of the incident photons, plants would have already solved the problem by developing the photosynthetic machinery, an almost perfectly efficient solar-to-chemical energy converter [5]. But the counting of photons entails not only their efficient absorption (hence, a dedicated pigment) but also other technical issues related to noise, sensitivity, and amplification.

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Rhodopsin-like proteins (rhodopsin from hereon) are dedicated light-absorbing pigments whose sensitivity (e.g., how well their molecule absorbs light) corresponds to a molar absorption coefficient ε of about 40–60,000 $M^{-1} \cdot cm^{-1}$ and an inherent noise (dark noise) approximately equal to zero. These values are at the best of the theoretical limits of any light-absorbing molecules [6,7].

The energy of an absorbed photon can modify only a single molecule, and this information cannot be conveyed beyond the point of absorption unless some sort of process transforms this tiny signal into a robust downstream signaling event, which will eventually increase the environmental sensitivity so critical for the survival and propagation of the species. This is the reason for the sophisticated process of amplification.

In the case of the photoreceptive process of microorganisms such as *Euglena*, knowledge of the amplification cascade that transforms the light perception in a cellular response is still incomplete and poorly understood, whereas the sequential amplification steps adopted by the visual system of higher organisms (e.g., the human eye) have been identified in almost all their details. In these systems, amplification is achieved by means of a cascade of nested reactions (the higher the number of nested reactions, the greater the amplification), each catalyzing the subsequent reaction [8–10].

In this paper, we describe the nonimaging photoreceptive process of *Euglena* and the visual imaging process of the human retina in their different biophysical aspects, analyzing the effect of quantum limitation on their efficiency and functioning.

2. Basic Concepts

According to Mayr, the complex macromolecules that make up living organisms are endowed with extraordinary characteristics, and many of them possess such a specific and peculiar ability to carry out a particular function that they emerge every time this specific function is demanded in animal and plant kingdoms [11]. Rhodopsin, with its role in photoreceptive and visual processes, is the perfect example of these function-defined macromolecules. Once this molecule appeared in the course of evolution, the bottleneck of light detection was passed; from then on, the challenge of "seeing" has been met by many different strategies. In evolutionary terms, these processes are an absolute terminal point; their sensitivity cannot be significantly enhanced as the laws of quantum physics impose a limit already reached by the photoreceptive system present in the very first forms of life (e.g., unicellular algae) and by the visual system of higher organisms (e.g., our eye), both using the same light-detecting molecule [11,12].

What is so special about rhodopsin? Rhodopsin has been extensively studied as a prototypical G-protein-coupled receptor (GPCR), characterized by seven helical segments that span the entire width of the membrane. This architecture is common to the most diverse receptor family in nature, i.e., the seven-transmembrane helix receptor family. These receptors are utilized in many other systems (olfaction, taste, and neurotransmission) and have been conserved over the course of evolution. Rhodopsin molecules consist of the opsin apoprotein (receptor) covalently bound to a retinal chromophore (ligand) via a protonated Schiff base linkage at the level of the seventh transmembrane segment. Upon absorption of a photon, the retinal isomerizes; this is the primary event of vision, which is considered one of the most evolutionarily optimized and fastest chemical processes (10^{-13} s). This isomerization initiates a series of conformational changes in the protein, converting it from the dark-adapted, inactive form to the light-activated form, which in turn triggers the amplifying cascade of reactions of the signaling pathway that eventually leads to light perception [8].

Rhodopsin has an intense absorption band (with a cross section of about 2×10^{-16} cm^2, near the maximum theoretical limit [13]) whose maximum can be tuned over the entire 380–640 nm range of the electromagnetic spectrum (visible radiation). The protein is characterized by a very high stability because in the absence of light, it can be activated only once every 10^{10} s by thermal energy, overcoming an energy barrier of 26 Kcal × mol^{-1} [14]. In a rod containing about 2×10^8 rhodopsin molecules, a spontaneous isomerization event

will occur about every 50 s [9,15]. The effect of this dark noise determines the threshold and the contrast of the system. In terms of quantum efficiency, the probability of rhodopsin isomerization once it has absorbed a photon is 0.7, at the best of the theoretical limit [8,9]. Moreover, as mentioned above, retinal isomerization produces remarkable structural changes, which can be associated with multiple protein domains because the Schiff base linkage moves approximately 5 Å with respect to the ring portion of the chromophore and pushes against the protein, converting the dark-adapted inactive form of the protein to the light-activated form [8].

As already mentioned, a bidimensional array of transmembrane rhodopsins represents the first photoreceptive device in evolution, characterized by a packing density of 20–30,000 molecules·μm^{-2} with an ε of 40–60,000 $M^{-1} \times cm^{-1}$ and a dark noise close to zero [2,9,12]. This simple photoreceptor was not accompanied by a pinhole aperture or a lens system; therefore, it was not an image-forming device. On the other hand, it did not suffer diffraction problems and could gather all the photons reaching its surface. A successive improvement of this rudimentary photoreceptor was the acquisition of a sort of sensitivity to light direction, entailing the possibility to change the cell movement direction. A dark screen positioned on the side of the photoreceptor fits the purpose, allowing the cell to perceive where the light comes from. A further step in photoreception evolution was the piling up of many layers of transmembrane photoreceptive proteins, which drastically improved the chance of gathering photons. Such a photoreceptor system is located close to an effector so as to transmit the information conveyed by the light directly to it [16].

These nonimaging photoreceptive devices are present in many microorganisms, such as *Euglena*, which can only discriminate between light and dark. As already mentioned, this flagellate is considered the starting point for the remote evolutionary origin of the eye [4,12,17].

Signal transmission by a photoreceptor requires either a potential difference or a chemical gradient. The comprehension of the actual amplification process in the photoreception systems of lower organisms is still incomplete, and the mechanisms behind it are far from being fully understood. The deceptive simplicity of these organisms does not necessarily imply the use of simple amplification processes.

The mechanism higher organisms use to amplify the first event of vision is indeed fully understood. As already stressed, an absorbed photon is converted into atomic motion, and this small perturbation is amplified over a million times to produce a reliable and reproducible signal that eventually reaches the synaptic terminals to initiate vision. As rhodopsin does not suffer from dark noise, the detection of incoming photons is by no way hindered [9].

At the first amplification step, light-activated rhodopsin triggers sequential Guanosine Diphosphate/Guanosine triphosphate (GDP/GTP) nucleotide exchange on its cognate heterotrimeric G protein transducin at a rate of about 1000 transducins per second. The binding of GTP to transducin leads to the release of R* for another round of catalysis, thus amplifying the signal over and over until its activity is shut off. The active form of transducin in turn activates the phosphodiesterase (PDE), a few tens for each photoisomerization. PDE is a powerful enzyme that very rapidly hydrolyzes cyclic GMP (cGMP), the intracellular messenger required for the membrane ion channels to remain open. This is the second amplification step; each PDE hydrolyzes multiple cGMP molecules, thus lowering the concentration of cGMP within the photoreceptor. This reduction leads to the closing of hundreds of channels, blocking entry of about a million Na^+ ions, thus hyperpolarizing the cell. This is the third million-fold amplification. Light-induced hyperpolarization is then passively transmitted by the receptor membrane to the synapses to give rise to the signal. The shutting off of activated rhodopsin requires binding to arrestin, which completely quenches rhodopsin activity. Upon quenching, all-trans-retinal is released and rhodopsin decays to the opsin apoprotein. Regeneration occurs by the binding of a new 11-cis retinal molecule, the opsin. Therefore, before a signal rises, the energy of the absorbed photon is multiplied and amplified over a million fold (Figure 1) [8,9,18,19].

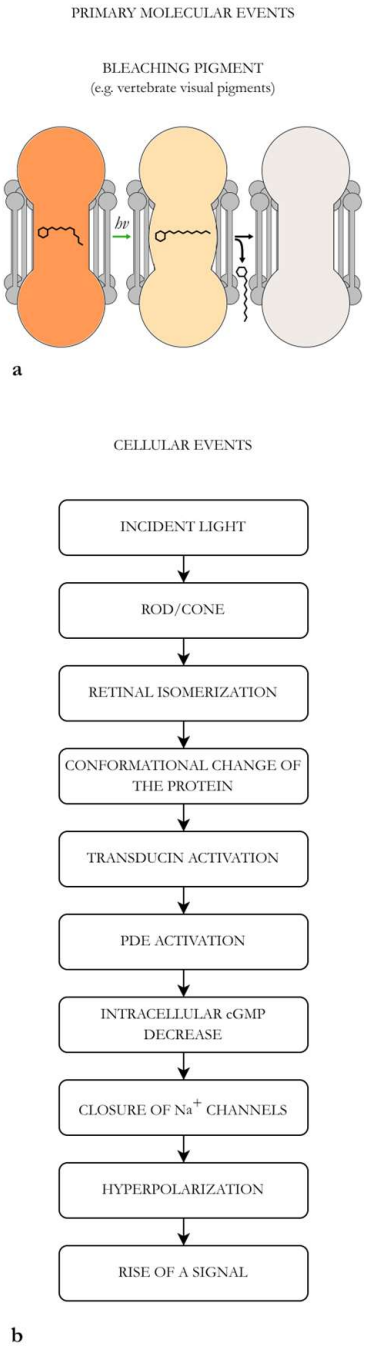

Figure 1. Molecular (**a**) and cellular (**b**) events of the phototransduction process in vertebrate visual systems. The different colors indicate the three different stages of rhodopsin. See text for details.

As in all biological systems, quantum electron transfer processes also occur in photoreceptive systems. Their description is outside the scope of this entry paper; theory and examples of these processes can be found in [20–23].

3. Nonimaging Photoreceptive Process

3.1. Structural Characteristics of a Photoreceptive Apparatus (e.g., Euglena gracilis)

The photoreceptive apparatus of *Euglena* consists of two distinct organelles: the screening device (eyespot) and the photoreceptor (PFB). The latter is an almond-shaped organelle of 2 μm length, consisting of stacked layers of membranes held together by interactions of the charged extramembrane domains of rhodopsin molecules arranged in a hexagonal lattice [15,16].

The photoreceptive protein of *Euglena* is characterized by optical bistability, i.e., it photocycles between two intermediates forms A and B photochemically but not thermically [24]. Under physiological conditions, form A is the dominant nonfluorescent intermediate with an absorption spectrum centered at 498 nm (A_{498}), while B is the fluorescent intermediate [25] that is energetically lower and more stable with an absorption spectrum centered at 462 nm (B_{462}) [26]. B_{462} can be considered the signaling state of the protein. The eyespot, always facing the photoreceptor inside the apical part of the cell, consists of a loose collection of globules containing carotenoids, whose absorption spectrum shows a unique and large band centered at 460 nm and matches the absorption spectrum of the B_{462} form [26].

3.2. Biophysics and Quantum Limitation of the Photoreceptive Process

In a typical day, 10^{17} photons $m^{-2} \cdot s^{-1} \cdot nm^{-1}$ are emitted by the sun and reach our planet. In water environments, absorption and reflection effects lower this figure to 10^{16}. This means that the simplest microalgal photoreceptor, consisting of a single layer of rhodopsin with 100 nm absorbance window, is reached by 10^6 photons$\cdot s^{-1}$ at most [27]. Only 0.01% of these photons are effectively absorbed; hence, the number lowers to 10^2. For swimming microalgae, which sample the light environment rotating with a frequency of 2 Hz, information on light direction results from the difference between the number of photons absorbed by the illuminated photoreceptor (for about 200 ms) and the number of photons absorbed by the photoreceptor that is 50% shaded by the eyespot This center dot is correct (for about 300 ms), i.e., about 10 photons$\cdot s^{-1}$. As experimentally demonstrated, this kind of photoreceptor possesses a threshold lower than 10 photons, and this small number of photons should be amplified to obtain a reliable signal [13]. In this single-layer photoreceptor, the amplification mechanism is similar to that of higher organisms [28,29]. Indeed, in the case of the crystalline photoreceptor of *Euglena*, consisting of 50 layers of photoreceptive membranes, 500 photon$\cdot s^{-1}$ are absorbed, and threshold and amplification mechanisms would necessarily follow different routes.

The threshold of *Euglena* photoreception has been measured by Ooka et al. (2014) [30], and a green light amount as low as 1 $\mu m \cdot W \cdot cm^2$ (about 10^4 photons $\mu m^{-2} \cdot s^{-1}$) is sufficient to induce a phototactic response. On the basis of the abovementioned assumptions (rotation frequency and shading) and taking into account a 10% glass reflection, about 800 photons trigger an *Euglena* photoresponse, a figure in line with the theoretical value.

3.3. Hypothesis on the Euglena Photoreceptive Mechanism

The core of the function of photoreceptors is the photodynamic equilibrium between the A_{498} and B_{462} intermediates of the sensor protein. If light directly impinges on the photoreceptor, A_{498} is the dominant intermediate. If the eyespot intercepts the light, UV and green light only reach the photoreceptor and the A_{498} intermediate converts to B_{462} (due to superimposition of the absorption spectra of the eyespot and the intermediate A_{498}). In turn, the newly formed B_{462} acts as an energy donor for the nearby protein in the A_{498} form, the energy acceptor, following a unidirectional Forster-type energy transfer (Figure 2) [31].

The photoswitch between the intermediates leads to a vectorial charge movement perpendicular to the photoreceptor membrane, producing a transient array of electric dipoles. Therefore, the *Euglena* photoreceptor could act as a phototransistor that transduces photon energy into an electric potential propagating distally through the flagellar structures (axoneme and paraxial rod) [32–35].

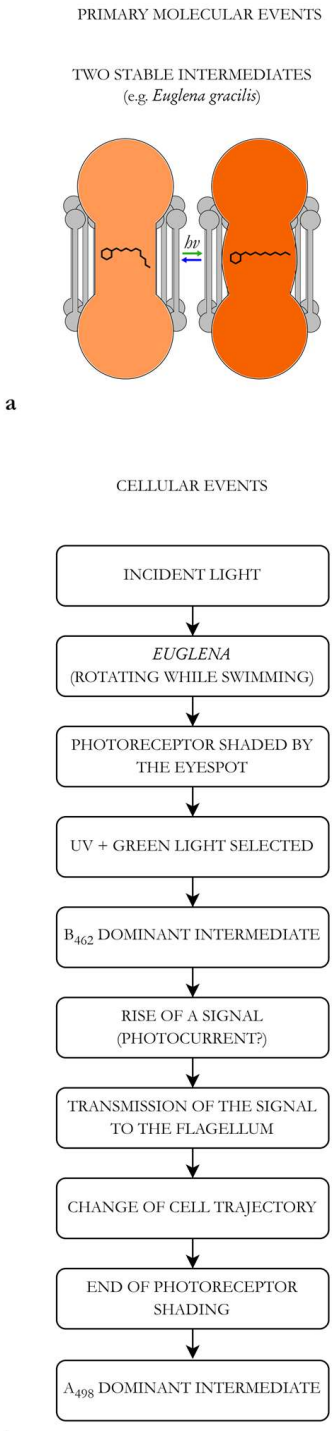

Figure 2. Molecular (**a**) and cellular (**b**) events of phototransduction process in the *Euglena* photoreceptive system. The different colors indicate the two different stages of rhodopsin See text for details.

4. Imaging Visual Process

4.1. Structural Characteristics of a Visual Apparatus (e.g., the Human Eye)

The human eye works like a camera, where the incoming light is refracted by a lens onto a light-sensitive back surface. Light enters the eye through the aperture lens system and is focused on the back wall. The lens, also known as crystalline lens, has a focal length of 16 mm and the aperture, i.e., the pupil, can expand or contract from a 2 mm (f/8, bright sun) to an 8 mm (f/2, vision threshold) diameter to adapt to light intensity.

Pupil adjustment needs tens of seconds [36–38]. The light-sensitive surface is the retina, a 10 cm^2 surface consisting of approximately 125 million photoreceptor cells spaced about 1 μm apart, rods, and three types of cones (blue, green, and red). The rods are highly sensitive black and white (intensity) sensors and are responsible for dim light vision and perception of size, shape, and brightness of visual images; the cones are color sensitive in the 390–780 nm wavelength range. The cones are highly localized in the central zone of the retina and the fovea, subtending about one degree, and are also present at low density all over the retina. The rods are localized all around the fovea. The cones set the limit of resolution to about 1–2 min of arc and match the diffraction disc of the 2 mm pupil slit [39,40].

The vitreous humor with a refractive index of 1.5 fills up the vitreous cavity between the lens and the retina. About half of the light entering the pupil is scattered or absorbed in the humor or the lens so that only about half reaches the retina. The exposure time (photon integration time) of the eye is about 0.2 s and increases by a factor 2 from high to low light [41,42].

4.2. Biophysics and Quantum Limitation of the Retinal Visual Process

The performance of the visual system is measured by the ratio between the information transmitted and the information contained in the incident light. To quantitatively assess the information conveyed by a finite number of photons, three aspects of the quantum limitation of the visual process need to be analyzed [1]: the finite number of incoming photons, their random distribution in time and space, and the false signals arising from this distribution and not from the original scene.

4.2.1. The Finite Number of Incoming Photons and Their Random Distribution in Time and Space

Let us look at an N pixel image consisting of uniformly spaced dots and containing a single gray dot having 99% brightness. To detect this spot and convey its information content, we need at least $100 \times (N - 1)$ photons: 100 photons for each of the pixels of the image minus the single gray spot (in a well-resolved image, the pixel range should be 10^6–10^7, and 10^8–10^9 photons are needed to precisely determine the location and brightness of the gray dot).

But this is not the way it works in daily life. As a matter of fact, photons reach the eye at random both in time and space, forming noise images with poor detection of fine details and low contrast. To analyze the effects of random photon distribution, we need to clarify the concepts of signal and noise. A signal can be defined as the average number of photons reaching a pixel. The noise is the root mean square (rms) deviation from this signal. The ratio between the signal and the noise (SNR) sets the accuracy with which the photon flux can be measured. For example, if the signal is N (i.e., N photons are detected), then the noise is $N^{1/2}$, and this is also the value of SNR. The threshold for visibility is set at SNR = 1.

In a real case, the actual number of photons reaching a pixel has an average value of 100, and the rms is equal to 10. Due to random photon distribution, the noise is 10 times greater than the signal we have to detect (1%), and the SNR is 0.1, far less than the threshold of visibility. Hence, we have to increase the number of photons reaching each pixel (i.e., the signal) to 10^4 in order to have an rms (noise level) of 1% and a satisfactory visibility threshold. A total of 10,000 N photons, randomly distributed in time and space in an N pixel image, are necessary to reveal the defined gray spot present in the image, i.e., in order to detect the fine details of an image, the number of photons conveying the information should be considerably increased.

4.2.2. False Alarm and Quantum Efficiency

False alarms are due to random photon distribution and are not intrinsic in the original image. To cope with false alarms, the signal should exceed the noise level by a factor k that is greater than 1, which depends on both the noise statistical distribution and the number

of observations. The factor k represents the number of times the noise rms must be added to the average value of the noise to assure that a noise fluctuation is not mistaken for the real signal, i.e., k increases the probability to assign an observation to the noise and not to the signal.

In the case of a 10^5 pixel image, we have 10^5 opportunities to generate a false alarm. To reduce the number of false alarms below the unit, we need a signal with an amplitude exceeding the noise fluctuation with a k value 4–5 times that of the noise rms plus the average noise. The photons required to detect a contrast C (C = 1 means 100% contrast, and C = 0.01 means 1% contrast) are expressed as follows:

$$\text{Photons} = k^2 \times N/C \quad (1)$$

$$\text{Photons}\cdot\text{cm}^{-2} = k^2 \times (C^2 \times (\text{area of pixel})^2)^{-1} \quad (2)$$

In the case of 10^{10} photons·cm^{-2}, we would be able to resolve black and pixels (100% contrast, C = 1) with a side of about 10^{-4} cm; however, with a contrast of 1% (C = 0.01), only pixels whose side is 10^{-2} cm can be resolved.

These statements would be true if the visual system counted every incident photon (100% quantum yield). To estimate the eye quantum efficiency, i.e., the fraction of incident photons that is actually used by the visual system, we have to assess the number of photons that strike each square centimeter of the retina.

Then, Equation (2) becomes the following:

$$\text{Photons}\cdot\text{cm}^{-2} = (k^2 \times \theta)/(C^2 \times (\text{area of pixel})^2 \quad (3)$$

where θ is the eye yield, which depends on the values of lens transmission (0.5), eye integration time (0.2 s), and pupil size (2–8 mm).

The eye quantum efficiency is difficult to accurately estimate. From a molecular point of view, only 50% of photons reaching a rod cell are absorbed, and only 70% of these photons eventually activate a rhodopsin molecule. The resulting 35% eye efficiency is then decreased to 10% by the factors listed above. This value has been experimentally confirmed, showing relatively small variations for light intensities ranging from the absolute threshold up to 10^8 times the threshold (from 5×10^{-13} to 5×10^{-5} W·cm^2·sr) [1,43].

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