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Phototransduction early steps model based on Beer-Lambert optical law

Ezequiel M. Salido *[,1], Leonardo N. Servalli *[,1], Juan Carlos Gomez, Claudio Verrastro

Group of Artificial Intelligence and Robotics, Universidad Tecnolgica Nacional, Av. Medrano 951, Capital Federal, Argentina

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ABSTRACT

The amount of available rhodopsin on the photoreceptor outer segment and its change over time is not considered in classic models of phototransduction. Thus, those models do not take into account the absorptance variation of the outer segment under different brightness conditions. The relationship between the light absorbed by a medium and its absorptance is well described by the Beer-Lambert law. This newly proposed model implements the absorptance variation phenomenon in a set of equations that admit photons per second as input and results in active rhodopsins per second as output. This study compares the classic model of phototransduction developed by Forti et al. (1989) to this new model by using different light stimuli to measure active rhodopsin and photocurrent. The results show a linear relationship between light stimulus and active rhodopsin in the Forti model and an exponential saturation in the new model. Further, photocurrent values have shown that the new model behaves equivalently to the experimental and theoretical data as published by Forti in dark-adapted rods, but fits significantly better under light-adapted conditions. The new model successfully introduced a physics optical law to the standard model of phototransduction adding a new processing layer that had not been mathematically implemented before. In addition, it describes the physiological concept of saturation and delivers outputs in concordance to input magnitudes.

1. Introduction

Vertebrate phototransduction is a process that takes place in the outer segment (OS) of the retina photoreceptors and consists of transforming light stimuli into electrical signals. The molecular events involved in this transformation constitute one of the biochemical sequences better understood in neuroscience. Forti, Menini, Rispoli, and Torre (1989) were the first to develop in detail an empirical model capable of simulating the phototransduction process for rod photoreceptors of the *newt triturus cristatus*. The Forti Mathematical Model (FMM) was enriched by various research teams obtaining highly accurate and detailed mathematical models (Dell'Orco, Schmidt, Mariani, & Fanelli, 2009; Hamer, 2000; Hamer, Nicholas, Tranchina, Lamb, & Jarvinen, 2005; Invergo, Dell'Orco, Montanucci, Koch, & Bertranpetit, 2014; Korenbrot, 2012; Lamb et al., 1992; Shen et al., 2010). The protein rhodopsin (R), localized in the OS of the photoreceptor, contains a chromophore called 11-cis-retinal. When this molecule absorbs energy from a photon, it changes its conformational structure and enters the all-trans- retinal state through a process called photoisomerization activating the rhodopsin molecule (R^*) (Farrens et al., 2010). In turn, active rhodopsins activate other molecules (transducins), generating a cascade effect which ends in current modulation (photocurrent) that flows through channels placed in the OS plasma membrane (Burns et al., 2001). The photoactivated rhodopsin is rapidly inactivated by successive phosphorylations and the binding to the soluble protein Arrestin. In this inactive state, the bleached rhodopsin (B) cannot activate transducin and it cannot be re-activated until it has completed a regenerative cycle. This cycle, known as the visual cycle, involves the reconfiguration of the bleached pigment all-trans- retinal to 11-cis- retinal in the retinal pigmented epithelium and its recombination with the opsin protein in the photoreceptor to generate a new activatable rhodopsin (Caruso et al., 2010; Fain, Matthews, & Cornwall, 1996; Fain, Matthews, Cornwall, & Koutalos, 2001; Nymark, Frederiksen, Woodruff, Cornwall, & Fain, 2012). This inactive period reduces the concentration of rhodopsin which can be activated in the OS, causing a decrease in the photoreceptor absorbtance and thus, a reduction in its sensitivity.

Since FMM, all phototransduction models have shared a common characteristic: the input stimulus in the equations is not light, but isomerizations of rhodopsin per second (Hamer et al., 2005; Invergo et al., 2014; Korenbrot, 2012). This precomputed stimulus omits the description of the rhodopsin photoisomerization through

* Corresponding authors.
E-mail addresses: ezequielsalido@gmail.com (E.M. Salido), leonardoservalli@gmail.com (L.N. Servalli).
[1] These authors contributed equally to this work.

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light absorption and ignores the fluctuations in the total number of rhodopsin in the OS, leading to an equation that responds linearly to different input stimuli (Torre, Forti, Menini, & Campani, 1990).

The Beer-Lambert law relates the absorption of light to the properties of the material through which the light travels. In this sense, the Beer-Lambert law can accurately determine the absorptance of the photoreceptor OS, which is the proportion of light absorbed by rhodopsin molecules (Warrant et al., 1998).

On the basis of these backgrounds, the objective of this work is to develop a mathematical model based on the biophysical processes involved in phototransduction that reflects the variation of photoreceptor absorptance under different lighting conditions. This new model (NM) also includes a scheme of rhodopsin bleaching and regeneration validated by van Hateren et al. (2007). The NM enables the extension of the operating range to handle light intensities of medium and high brightness levels, in which the empirical FMM does not respond properly. Also, the modular design of the NM enables it to be used in cone or rod photoreceptors of any species of vertebrates.

2. Theoretical section

This section briefly reviews the FMM and analyzes the implementation of the Beer-Lambert law and the Van Hateren visual cycle equation.

2.1. The model of Forti

Forti et al. described the phototransduction process from photoisomerizations per second ($J_{hv}(t)$) to photocurrent (J), based on a sequence of events described by the following differential equations:

$$\dot{R}^* = J_{hv}(t) - \alpha_1 R^* + \alpha_2 B \tag{1}$$

$$\dot{B} = \alpha_1 R^* - (\alpha_2 + \alpha_3) B \tag{2}$$

$$\dot{T}^* = \epsilon R^* (T_{Tot} - T^*) - \beta_1 T^* + \tau_2 PDE^* \tag{3}$$

$$\dot{PDE}^* = \tau_1 T^* (PDE_{Tot} - PDE^*) - \tau_2 PDE^* \tag{4}$$

$$\dot{c} = bJ - \gamma_{Ca}(c - c_0) - k_1(e_T - c_b)c + k_2 c_b \tag{5}$$

$$\dot{c}_b = k_1(e_T - c_b)c - k_2 c_b \tag{6}$$

$$\dot{g} = \frac{A_{max}}{1 + (\frac{c}{K_c})} - g(V + \sigma PDE^*) \tag{7}$$

$$J = J_{max}\frac{g^3}{g^3 + K^3} \tag{8}$$

Where R^* and B are the concentration of active and inactive rhodopsin respectively, T^* and T_{Tot} are the concentration of activated and total transducin, and PDE^* and PDE_{Tot} are the concentration of active and total phosphodiesterase. In turn, C is Ca^{++} concentration in the OS, while C_b is Ca^{++} buffer concentration; g is GMPc concentration and J is the current flowing through the Na^+ GMPc-dependent channel, called photocurrent. The constants used in this work are those described by Forti and later adjusted by Kamiyama, Ogura, and Usui (1996). The experimental data are taken from Forti's work (Forti et al., 1989).

2.2. Construction of a new mathematical model

The Beer–Lambert law describes the relationship between the light that is absorbed in a given material medium and the characteristics of the medium as light passes through it. The proportion of light absorbed by the material medium as light passes through it, is called absorptance (A) and is defined by the Beer-Lambert law as a function of the molar extinction coefficient (α), the concentration of absorbing substance (c) and the distance the light must travel (l), as per the following expression.

$$A = 1 - e^{-\alpha c l} \tag{9}$$

In the photoreceptor, the absorbing substance concentration (c) is determined by the number of activatable rhodopsin molecules (R) contained in the volume of the photoreceptor OS, established by the transversal section area (a) and the length of the OS (l). The concentration is defined, as follows:

$$c = \frac{R}{al} \tag{10}$$

Through Eq. (9), the absorptance of the photoreceptor OS can be calculated, thus allowing the proportion of light absorbed by R molecules contained in the photoreceptor to be determined (Warrant et al., 1998). The quantum efficiency of 11 cis-retinal is the percentage of photons that will produce an effective photoisomerization when reaching the 11-cis-retinal molecule. Eq. (11) shows the relationship between axial incident photons in the photoreceptor OS per unit of time (I), absorptance and quantum efficiency (ϕ), whose product determines active state rhodopsin production (R^*). The same equation further expresses R^* decay towards an inactive state determined by constant τ_R, which defines the lifespan of R^*.

$$\dot{R}^* = I(1 - e^{-\alpha c l})\Phi - \frac{R^*}{\tau_R} \tag{11}$$

The bleaching and regeneration cycle consists of a mechanism whereby rhodopsin molecules in a non-activatable state (B) are regenerated in order to enter an activatable state (R). These molecules are recruited to the OS to become part of the activatable rhodopsin concentration (Lamb et al., 2004; Mahroo et al., 2004). The mechanism may be expressed as follows:

$$\dot{B} = \frac{R^*}{\tau_R} - \frac{B}{\tau_B}\frac{K_B}{B + K_B} \tag{12}$$

The first term is associated with R^* decay, while the second term describes the pigment regeneration from an inactive state in a variable τ_B time that mainly depends on the semisaturation constant K_B (van Hateren et al., 2007). New differential equations (Eqs. (11) and (12)) are used to replace Forti empirical equations (Eqs. (1) and (2)) and are also integrated into the remaining chain of equations described by Forti with a single change in Eq. (3) where the activation of 150 transducins per second for every activated rhodopsin was added (Leskov et al., 2000). Parameters used in Eqs. (11) and (12) are described in Table 1.

In order to convert the experimental and theoretical stimuli used by Forti from photoisomerizations per second to photons per second, we used the inverse of the original equation described by Cobbs et al. (1987). The parameters used for rod construction in the NM are the same as those used by Forti in his mathematical model: Collecting Area, 20 [μm^2]; quantum efficiency, 0.67 [no unit]; and rod radio, 5.5 [μm].

The computations for this article were performed using Matlab software. The system can be described as a series of coupled ordinary differential equations, which can be solved using a standard ODE solver. The Matlab code that implements this scheme is available in the url: http://dx.doi.org/10.5281/zenodo.45365.