November 2, 2014

**Model for primate cone responses**

This is a description of our current model for the outer segment membrane currents of primate cones. The model is able to capture several nonlinear properties of the cone responses - including increment/decrement asymmetries, and both rapid gain control and slower changes in mean current following a light step. It is based on the canonical description of the transduction cascade with an added slow calcium-dependent modulation of the relationship between cGMP concentration and membrane current.

## Model architecture

Photopigment activity $R$ is modeled by low-pass filtering the stimulus $s$:

$$dR(t)/dt = s(t) - \sigma R(t) \tag{1}$$

where $\sigma$ is the rate constant (1/time constant) for the decay in photopigment activity. Note this measures the stimulus in units of rhodopsin activity - adding an extra scale factor in front of $s$ would free up its units, so it could be, e.g., in isomerizations per sec (or some god-awful psychophysical unit like trolands or trolls or something).

PDE activity $P$ is generated by low-pass filtering the photopigment activity:

$$dP(t) = R(t) + \eta - \phi P(t) \tag{2}$$

where $\eta$ is the rate constant for spontaneous PDE activation and $\phi$ is the rate constant for decay. When $R = 0$, $P = \eta/\phi$, which is an important determinant of the time course of the flash response in the dark. A note here on units. PDE activity is in $\text{sec}^{-1}$ (from equation below for cGMP concentration). This means the photopigment (and stimulus) activity is in $\text{sec}^{-2}$ to be consistent. This is a bit odd for the stimulus, so it is probably better to add the extra scale factor above and specify the stimulus in more conventional units.

Cyclic GMP activity $G$ is dictated by a balance of the rate of creation (by guanlylate cyclase) and destruction (by PDE):

$$dG(t)/dt = s(C) - P(t)G(t) \tag{3}$$

where $s$ is the rate of cGMP creation, which depends on the calcium concentration $C$. From this equation it is clear the units of $P$ have to be $\text{sec}^{-1}$ ($G$ will be in standard units of concentration - M - and then $s$ in $\text{Msec}^{-1}$).

The calcium concentration depends on calcium entry and calcium extrusion.

$$dC(t)/dt = qI(t) - \beta C(t) \tag{4}$$

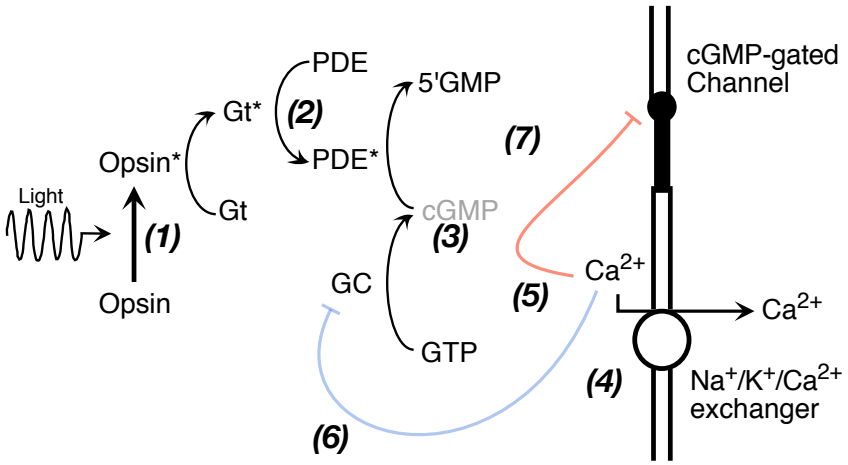


Figure 1:

where $I$ is the membrane current, $q$ accounts for the fraction of the current carried by calcium and the outer segment volume, and $\beta$ is the rate constant for calcium extrusion.

We also introduced a 'slow' calcium variable $C_s$ that is a derived from the calcium concentration:

$$dC_s(t)/dt = -\beta_s(C_s(t) - C(t)) \tag{5}$$

$C_s$ will track $C$, but filtered through the rate constant $\beta_s$.

The cGMP creation rate depends on calcium as

$$s(C) = \frac{s_{max}}{1 + (C/K_s)^n} \tag{6}$$

where $s_{max}$ is the maximal rate, $K_s$ is the half-maximal calcium concentration (i.e. when $C = K_s$, $s = s_{max}/2$), and $n$ is an exponent that determines the steepness of the relation between $s$ and $C$.

The membrane current is given by

$$I(t) = \frac{kG^m(t)}{1 + C_s/C_d} \tag{7}$$

where $k$ is a constant, $m$ is an exponent account for a nonlinear dependence of current on cGMP, and $C_d$ is the dark cGMP concentration. The role of $C_s$ here is to alter the relation between cGMP and current, such that when $C_s$ drops, a given cGMP concentration produces more membrane current. This causes $C_s$ to counter the effects of light: light increases upstream stuff, decreasing $G$ and $I$, causing $C_s$ to slowly decrease, which then counters part of the initial decrease in $I$.

### Model parameters

This model relates the stimulus $s(t)$ to the current $I(t)$ through a set of parameters. Nominally those are: $\{\sigma, \eta, \phi, q, \beta, \beta_s, s_{max}, K_s, n, k, m, C_d\}$. It is also useful to introduce $G_d$ as it links many

of the other parameters. Some of these can be eliminated via experiment. Thus from Eq. 7 the dark current (directly measured from experiment) is

$$I_d = kG_d^m/2. \tag{8}$$

In rods, $m = 3$, $C_d \approx 5 \times 10^{-7}$ M, $n = 4$, $k \approx 1 \times 10^{-2}$pA/$\mu$M$^3$. That eliminates 5 of the 13 parameters (including $G_d$) above.

Two of the remaining constants can be eliminated via steady state relationships. From Eq. 4

$$q = C_d\beta/I_d, \tag{9}$$

and from Eq. 2 and 6

$$s_{max} = (G_d\eta/\phi)(1 + (C_d/K_s)^n). \tag{10}$$

This leaves 6 free parameters $\{\sigma, \eta, \phi, \beta, \beta_s, K_s\}$ (we have sometimes also allowed $G_d$ to vary).

Some of these remaining parameters are constrained by experiment (even if not directly measured). Thus $\beta \approx 25 - 100$ per sec, $K_s \approx C_d/2$, $\sigma \approx 50 - 200$ per sec, $\phi \approx 50 - 200$ per sec.