BIOPHYSICAL EVIDENCE THAT LIGHT ADAPTATION IN *LIMULUS* PHOTORECEPTORS IS DUE TO A NEGATIVE FEEDBACK

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ABSTRACT The steady-state stimulus–response curve of the *Limulus* ventral photoreceptor comprises a linear portion followed by a less-than-unity power law dependence, which is maintained over at least 4 decades of intensity. This progressive desensitization corresponds to light adaptation. For flash stimulation of dark-adapted cells, the stimulus–response curve again has an initial linear portion, but this is followed by a region of supralinearity before the curve saturates. In a previous article, we showed that the distribution of time integrals of the single-photon responses is consistent with a model of a single chain of first-order reactions. Starting with such a model, we have looked at relevant elementary nonlinear biochemical mechanisms to determine which of them can modulate the enzymatic amplifications of the chain in such a way as to lead to these behaviors. We assume that each of the two phenomena, adaptation and supralinearity, derives from a single mechanism that acts on a single enzymatic stage. We then conclude that the adaptation must be a cooperative negative feedback, in which an accessory material activated by a late stage of the transduction chain acts cooperatively to inhibit an earlier enzymatic amplification. In *Limulus*, the number of molecules that cooperate is between 3 and 5. We were not able to discard any of the mechanisms tested for the supralinearity, except to say that they must act at a stage of the chain later than that on which the adaptive material acts. If we assume the conclusions of a previous work which shows that the supralinearity mechanism is active during the steady state, we can also conclude that the supralinearity stage must precede the stage that is the source of the adaptive material.

INTRODUCTION

The range of steady intensities of a light stimulus over which photoreceptor cells respond differentially can extend across at least 6 decades. However, the range of their neural response amplitudes is limited to 2 or 3 decades. To encompass the intensity information contained in natural stimuli, the photoreceptors of all invertebrates checked so far perform a power law transformation:

$$R = aI^{\sigma}, \tag{1}$$

where R is the response amplitude, I is the stimulus background intensity, σ and a are constants, and $0 < \sigma < 1$. This relationship is achieved by the nonlinear process of "light adaptation" and is maintained over a wide range of intensities following an initial linear portion. Two approaches have been used to determine the value of σ. The first is the measurement of steady-state stimulus–response curve, which gave the following values for σ: In the lateral eye of *Limulus* 0.5 (Dodge et al., 1968); in the ventral photoreceptor of *Limulus* 0.3 (Wong et al., 1982); and in *Drosophila* 0.35 (estimated by us from the data of Wu and Pak, 1978). The second approach is the measurement of the dependence of the sensitivity (the amplitude of the response to a fixed small incremental test flash divided by the number of photons in the flash) on the background intensity. Values of σ obtained are: In *Erythrocephala* 0.2 (Zettler, 1969); in *Phormia regina* 0.2 (French, 1979); and in locust, 0.18 (Howard, 1981). Thus σ determined by both techniques and in all preparations lies between 0.18 and 0.5.

If we assume that photoreceptor responses are made up of elementary events ("bumps") whose properties change with light intensity, it is possible by noise analysis to measure these changes. (These bumps are believed to be the responses to absorption of individual photons.) It is found that the departure from proportionality between R and I corresponds mainly to a decrease with increasing intensity of the average amplitude of the underlying bumps with little change in quantum efficiency and time course (Dodge et al., 1968; Wu and Pak, 1978; Wong et al., 1982).

Another strong nonlinearity seen in *Limulus* is the supralinear dependence on intensity of the responses of dark-adapted cells to flashes (Brown and Coles, 1979).

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Here too, the bump amplitude is the main affected parameter (Grzywacz et al., 1987).

The bump amplitude is determined by the degree of amplification of the process coupling the absorption of a photon to the opening of multiple ionic channels in the cell (Cone, 1973). The main objective of the present work is a biophysical characterization of the mechanisms that can modulate the amplification process and control the bump size under light adaptation. We will show that the power law, as expressed in Fig. 1 for the *Limulus* ventral photoreceptor, places a strong constraint on these mechanisms.

EXPERIMENTAL METHODS AND RESULTS

The preparation used in this investigation was the ventral photoreceptor of *Limulus*. Complete and reliable experiments were performed in five cells. The methods of the preparation are described elsewhere (Grzywacz et al., 1987). The experiments were performed at room temperature, 18°–23°C. The cells were voltage-clamped at their resting potentials (−45 to −65 mV).

In the present experiment, the computer sampled the signals at 3.91-ms intervals, and the averages of 256 such consecutive samples, or 1 s of signal, were stored. This procedure corresponded to inserting a low-pass filter.

After successful cell penetration, the photoreceptor was allowed to dark-adapt for 30 min. Then very low intensity 30-s steps of light were presented to the cell and the intensity found which resulted in an average of ~1 bump/s; we call this intensity I_0. The experiment then consisted in repeated series of six runs. Before and after each run by 1 s, 1-s patches of signal were averaged, and the average of the two was used as a baseline. This procedure was used to take into account the small and slow contributions of the electrogenic sodium pump (Brown and Lisman, 1972; Wong et al., 1982). In each run, a step of light was delivered. The light was maintained until 512 averaged points were recorded (~8 min) and then turned off. In the first run, the light intensity was I_0, and for the other runs the light intensity was increased successively by 1 log unit. The highest light intensity used was 5 log units higher than I_0. The time between runs within a series was not monitored. Between consecutive series, 15 min were allowed for dark adaptation.

Fain and Lisman (1981) point out that the "steady-state" response in voltage-clamped *Limulus* cells often falls slowly with time. We recorded long periods of the response to be able to measure the "real" steady-state response amplitude. The responses were found to stabilize after ~5 min of illumination, and only the final stabilized level was used.

After the experiments the response amplitude in the stable period was averaged, and the results were plotted as a function of the light intensity on a log-log scale. For the cells reported in these experiments, the averages for a given light intensity in two consecutive series never differed by more than 10%.

The result for one cell is shown in Fig. 1. The slope of the line linking the response for the two smallest intensities is ~1.1 (pooled results from five cells, 0.91 ± 0.15 SD). The slope of the line through the next 4 log units of light intensity is 0.16 (pooled results, 0.20 ± 0.03). The lines were fitted by eye. The slope 0.16 represents a power law of the type expressed in Eq. 1 with $\sigma = 0.16$ (A possible source of the difference between our values and those of Wong et al. [1982] may be their having measured the response amplitude at much shorter times after the onset of the steady stimulus.)

THEORY

We present a systematic analysis of all possible models for the steady-state stimulus–response curve constrained as follows:

(*a*) We start with a transduction chain consisting of fixed-gain steps and of first-order enzymatic amplifications, following Borsellino et al. (1965) and Borsellino and Fuortes (1968). Grzywacz and Hillman (1985) showed that the distribution of the time integrals of isolated, dark-adapted bumps in *Limulus* is experimentally close to exponential and that this is consistent with the biochemical chain's being composed of linear reactions only (that is, reactions with first-order kinetics). Such a chain is represented in Scheme 1.

$$Rh \rightarrow E_1 \rightarrow E_2 \rightarrow \ldots \rightarrow E_i \rightarrow E_{i+1} \rightarrow \ldots \rightarrow E_p.$$
$$\qquad\qquad\qquad\qquad\quad S$$

Scheme 1

In the scheme, absorption of a photon by a rhodopsin molecule triggers a chain of chemical reactions, which leads to the opening of the channels E_p. The passage

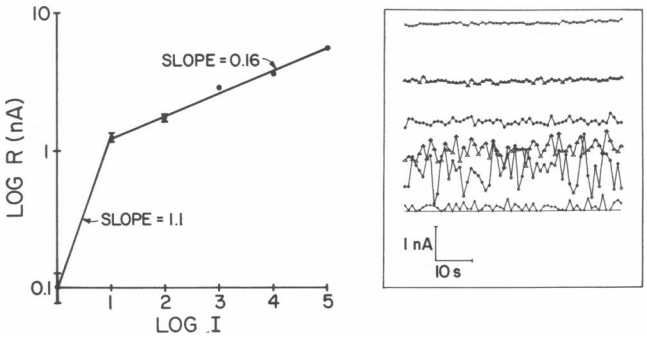


FIGURE 1 The experimental steady-state intensity–response curve. The figure shows a log-log plot of the steady-state response amplitude against intensity for a *Limulus* ventral photoreceptor. The inset shows a typical set of recordings after 1 s averaging as described in the text. The size of the vertical bars shows the standard error of the recorded amplitude. Note that after a slope of ~1 at the low intensities, a fractional power law is established at high intensities with a slope of 0.16. Similar curves, with an average high-intensity slope of 0.20, were obtained in five cells. Of the models illustrated in the following figures, only those families of which Figs. 9 and 10 are examples can fit these data.

$E_i \rightarrow E_{i+1}$ is shown as one that gives signal amplification through the continuing action of an enzyme, and there may be several such stages. Each enzyme is assumed to have a finite lifetime. E_i transforms the substrate S into its product form, E_{i+1}. First-order kinetics implies that the concentration of S during the single-photon response remains constant.

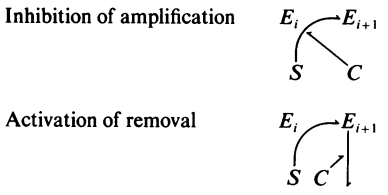
(*b*) We insert into this chain mechanisms to account for the observed nonlinearities of the response that appear at higher intensities, the light adaptation and the supralinearity. Each of these mechanisms is assumed to act on a single enzymatic stage.

(*c*) Light adaptation is known to be intermediated by an internal messenger, probably Ca^{++} (Lisman and Brown, 1972, 1975). We therefore limit the models considered to those in which the adaptation involves the action of an antagonistic agent on an enzymatic stage. This consideration eliminates models with saturation, in which one material essential to the transduction is depleted (as in Knight, 1973, and Carpenter and Grossberg, 1981).

We will now consider separately models for adaptation and for supralinearity and then combine them.

Models for Adaptation

Let the enzymatic stage on which the adaptation agent acts be the transition $E_i \rightarrow E_{i+1}$ shown in Scheme 1. Light adaptation corresponds to a decline in bump size. Thus we must suppose a decrease in the $E_i \rightarrow E_{i+1}$ amplification. Scheme 2 shows the possible mechanisms considered for this modulation:



Scheme 2

In the inhibition case, some material C appears inside the cell as a result of the stimulation and inhibits the amplification (e.g., by competitive inhibition). In the activation case, some material C appears inside the cell and activates the removal of the product of the reaction. We have not found a way of distinguishing between the inhibition and activation possibilities and thus shall relate only to the inhibition. The source of C will be discussed later.

In this paper, we will assume that the inhibition of the enzymatic reaction is competitive. The results are not substantially different for noncompetitive inhibition. The chemical equations are:

$$S + E_i \underset{k_2}{\overset{k_1}{\rightleftharpoons}} E_iS \xrightarrow{k_3} E_i + E_{i+1} \tag{2a}$$

$$E_{i+1} \xrightarrow{k_4} \tag{2b}$$

$$nC + E_i \underset{k_6}{\overset{k_5}{\rightleftharpoons}} E_iC_n. \tag{2c}$$

Note that in general, we allow C to affect the enzyme cooperatively, that is, E_i has n binding sites for C, which when fully occupied cause E_i's inhibition. Let E_0 be the total concentration of E_i in all its forms E_i, E_iC_n, and E_iS. We assume E_0 to be proportional to light intensity:

$$E_0 = \gamma I. \tag{3}$$

The necessary assumption for the validity of this equation is that the decay of E_i is unaffected by its being bound. The steady-state equations derived for Eq. 2 are:

$$E_0 = [E_i] + [E_iS] + [E_iC_n] \tag{4a}$$

$$k_6[E_iC_n] = k_5[E_i][C]^n \tag{4b}$$

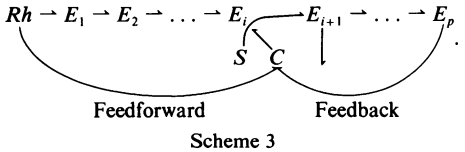
$$(k_2 + k_3)[E_iS] = k_1[S][E_i] \tag{4c}$$

$$k_4[E_{i+1}] = k_3[E_iS], \tag{4d}$$

where from our assumptions $[S]$ is constant, $[S] = S_0$. These are four equations in four variables that together with Eq. 3 can be solved for $[E_{i+1}]$ as a function of I. In the present discussion, we assume that the only nonlinearity occurs at $E_i \rightarrow E_{i+1}$, thus the response $R = \delta[E_{i+1}]$, where δ is a constant. It follows that we can calculate the dependence of R on I:

$$R = \frac{\left(\frac{\delta\gamma k_6 k_1 k_3 S_0}{k_4 k_5 (k_2 + k_3)}\right) I}{\left(\frac{k_6}{k_5} + \frac{k_6 k_1 S_0}{k_5 (k_2 + k_3)}\right) + [C]^n} = \frac{A'I}{B' + [C]^n}. \tag{5}$$

(In this paper A', B', F', A, B, F, and G are constants, which depend only on the constants of the chain's chemical equations, and which may change their definitions with each use.) To determine how R depends on I, it is necessary to know how $[C]$ depends on R. We suppose that C is created by a stage of the chain itself, and not by a separate process. Because of our assumption that the only nonlinearity occurs at the enzymatic amplification stage $E_i \rightarrow E_{i+1}$, it follows that there are two possible distinct sources of C, before or after the amplification:



Scheme 3

We assume that the concentration of free C is always much greater than that of the C bound to E_i. This applies to all the models of this article. In the feedforward case, $[C]$ is therefore proportional to light intensity. Thus, Eq. 5 yields

an equation of the form

$$R = \frac{AI}{B + I^n}. \tag{6}$$

This result is sketched in Fig. 2.

The responses are linear for low light intensities. The behavior for high intensities depends on n. If $n = 1$ the curve approaches saturation for large I. If $n > 1$, the denominator of Eq. 6 rises faster than the numerator, causing R to fall with I. No fractional power law appears (Eq. 1 and Fig. 1).

In the feedback case, $[C]$ is proportional not to the light intensity but rather to the response. This leads to an equation of the form

$$R = \frac{AI}{B + R^n}. \tag{7}$$

This type of response has the behavior sketched in Fig. 3. For low-light intensities, where the response is small, $B \gg R^n$, and the response is proportional to light intensity. For sufficiently high light intensities, $R^n \gg B$, and

$$R = A^{1/(n+1)} I^{1/(n+1)}, \tag{8}$$

so that the response passes from a linear behavior to a power law as in Eq. 1 with $\sigma = 1/(n + 1)$.

In summary, up to this point we have shown that a model having a negative feedback which cooperatively controls a single enzymatic amplification is consistent with the observed high-intensity power law. A negative feedforward is not.

Models for Supralinearity

The observation of supralinearity implies the existence in the cell of another mechanism that modulates an enzymatic amplification process, this time increasing it. Let this amplification be in an $E_j \rightarrow E_{j+1}$ transition within the transduction chain. How does the existence of such a mechanism affect the results discussed above?

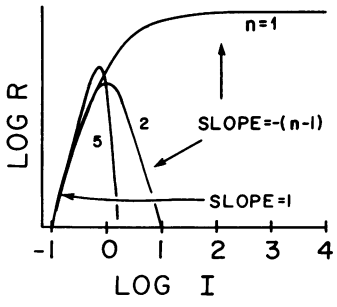


FIGURE 2. The negative-feedforward model for adaptation. This figure describes the prediction of the steady-state response (R) versus intensity (I) curve for a mechanism in which an accessory material appears in a feedforward manner and cooperatively inhibits the activity of an enzyme. That is, there are n binding sites in the enzyme that when occupied by the accessory molecules inhibit the enzymatic activity. Its behavior is described by Eq. 6. Here, $B = 1$ and the value of A is irrelevant, since it moves the entire curve vertically. As in all our examples, the slope of the curve is 1 at low intensities. Note that this type of mechanism does not predict a fractional power law increase of R with I, but instead predicts an integral power law decrease at high intensities for $n > 1$.

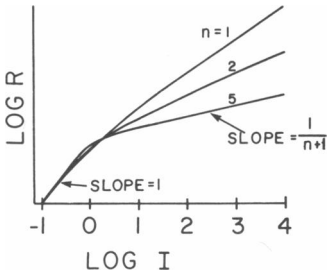
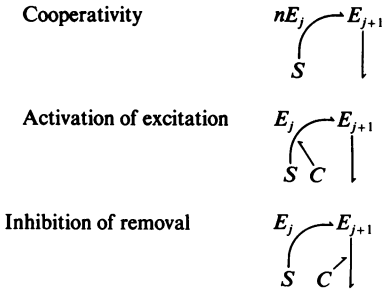


FIGURE 3. The negative-feedback model for adaptation. As in Fig. 2 but for the mechanisms in which an accessory material appears in a feedback mode and inhibits the activity of an enzyme; Eq. 7. Here $B = 1$ and the value of A is irrelevant. Note that this type of mechanism predicts a fractional power law behavior in the high-intensity range.

We first study in isolation the mechanisms by which an enzymatic process could be modulated to produce supralinearity, and later combine these with the adaptive process in the same chain. The possibilities of enhancement in an enzymatic process are shown in Scheme 4.



Scheme 4

The cooperative action of nE_j molecules in the chain can clearly produce a supralinear behavior in the flash response. This is the first possibility of the scheme. In the two other possibilities, a material C appears and either activates the excitation reaction itself or inhibits the removal of the product of the reaction. As before we have been unable to find a way of distinguishing between these two possibilities, and here we examine only the activation of excitation. Also as before, the material C may appear in either a feedforward or a feedback path.

In the cooperative case, n molecules of E_j act together to accelerate the $S \rightarrow E_{j+1}$ reaction. The apparent linearity of the isolated bump processes (Grzywacz and Hillman, 1985) suggests that the reaction is linear at low intensities. This implies that the cooperativity is not absolute, that is, the reaction can take place even when one molecule of E_j is present. The chemical equations are

$$S + nE_j \xrightarrow{k_1} nE_j + E_{j+1} \tag{9a}$$

$$S + E_j \xrightarrow{k_2} E_j + E_{j+1} \tag{9b}$$

$$E_{j+1} \xrightarrow{k_3}. \tag{9c}$$

For the sake of simplicity, we disregard the cooperation of more than 1 and less than nE_j molecules. This form of

simplification will be used throughout the paper. Here, we again suppose the concentration of S to be a constant, S_0, and the concentration of E_j to be given by a relation similar to Eq. 3. The steady-state equation is

$$k_1[S][E_j]^n + k_2[S][E_j] = k_3[E_{j+1}], \tag{10}$$

which can be expressed in terms of R and I:

$$R = AI^n + BI. \tag{11}$$

If $n > 1$, then for very low-light intensities $AI^n \ll BI$, and the response is linear with the light intensity. For high intensities $AI^n \gg BI$, and the response is supralinear. This behavior is shown in Fig. 4.

In the second possibility of Scheme 4, the material C enhances the enzymatic activity of E_j. The molecule E_j has n binding sites for C which accelerate the activity of E_j when fully occupied. However, the linearity of the bump processes (Grzywacz and Hillman, 1985) suggests that either E_j can carry on its reactions, at least slowly, without the help of C, or that C has a non-zero resting concentration. The two alternatives make the same predictions, so we refer only to the first. The chemical reactions are

$$S + E_j \xrightarrow{k_1} E_j + E_{j+1} \tag{12a}$$

$$S + E_jC_n \xrightarrow{k_2} E_jC_n + E_{j+1} \tag{12b}$$

$$E_{j+1} \xrightarrow{k_3} \tag{12c}$$

$$nC + E_j \underset{k_5}{\overset{k_4}{\rightleftharpoons}} E_jC_n, \tag{12d}$$

where we assume $k_2 \gg k_1$. The steady-state equations are

$$E_0 = [E_j] + [E_jC_n] \tag{13a}$$

$$k_1[S][E_j] + k_2[S][E_jC_n] = k_3[E_{j+1}] \tag{13b}$$

$$k_4[C]^n[E_j] = k_5[E_jC_n]\ . \tag{13c}$$

If E_0 is proportional to light as in Eq. 3, we obtain an $R - I$ equation of the form

$$R = \frac{(A' + B'[C]^n)I}{F' + [C]^n}. \tag{14}$$

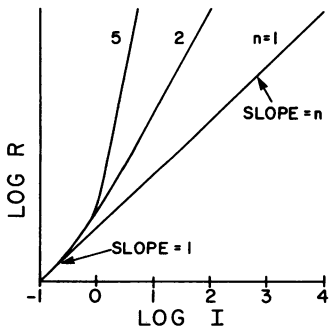


FIGURE 4 The cooperativity model for supralinearity. As in Fig. 2 but for the mechanism in which enzyme molecules of a certain type cooperate in order to act; Eq. 11. Here $A = B = 1$. Note the supralinearity predicted for the high intensities and $n > 1$.

For the feedforward case, $[C]$ is proportional to light intensity, whence

$$R = \frac{AI + BI^{n+1}}{F + I^n}. \tag{15}$$

This equation has an interesting behavior. For low I, $F \gg I^n$, $AI \gg BI^{n+1}$, and the response is proportional to light. At higher intensities, because $k_2 \gg k_1$, one can show that $BI^{n+1} \gg AI$ before I^n becomes greater than F. In this case, following a linear regime, the response behaves as I^{n+1}. For very high light intensities $I^n \gg F$, and R is again linear with light. The linear dependence of R on I at high intensities corresponds to the saturation of the feedforward process. The behavior of Eq. 15 is shown in Fig. 5.

For low and intermediate intensities, this kind of curve behaves similarly to the cooperative case (Fig. 4), but with slope $n + 1$ instead of n.

For the positive-feedback case, we use Eq. 14 and the assumption that $[C]$ is proportional to the response to get an equation of the form

$$R = \frac{AI + BR^nI}{F + R^n}. \tag{16}$$

For low-light intensities, the response is small and so $R^n \ll F$ and because BR^nI has a higher power dependence on I than AI, we can say that $BR^nI \ll AI$. The response is then linear with light intensity. At very high intensities, the response is again proportional to intensity ($BR^nI \gg AI$ and $R^n \gg F$). As in the case of the positive feedforward, $k_2 \gg k_1$, and for intermediate intensities one can show that BR^nI passes AI before R^n passes F, which gives rise to a supralinear behavior and a discontinuity at intermediate

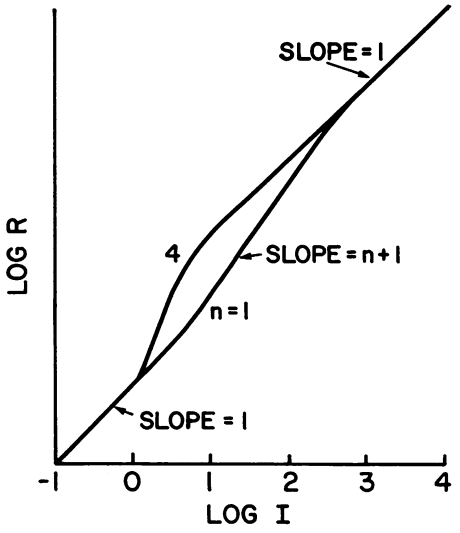


FIGURE 5 The positive-feedforward model for supralinearity. As in Fig. 2 but for the mechanism in which an accessory material appears in a feedforward manner and enhances the activity of an enzyme; Eq. 15. In the plots, $A = B = 1$ and $F = 100$. Note that this type of mechanism predicts a supralinear behavior for intermediate intensities and $n > 1$, and a linear high-intensity behavior.

intensities as shown in Fig. 6. The source of the discontinuity is the autocatalytic feedback, which leads to an uncontrolled amplification until the enzyme is saturated with cofactor, after which the response again depends linearly on intensity. (It is not possible to rule out positive feedback on the grounds that this discontinuity is not observed experimentally. The autocatalytic explosion may not occur in the flash responses, because the rise of the enzyme concentrations is transient. On the other hand, in steady state, light adaptation may suppress the expression of the positive feedback. These possibilities will be discussed in the next section.)

In summary, isolated mechanisms that lead to a supralinear dependence of response on stimulus at intermediate intensities are: cooperativity, positive feedforward, and positive feedback, the latter two acting cooperatively. (We note, however, that Grzywacz et al. [1987] showed that the mechanism responsible for flash supralinearity probably is not a pure cooperativity.)

Models with Both Adaptation and Supralinearity

We now turn to an analysis of the effects the insertion of a mechanism for supralinearity would have on the models for adaptation discussed above; in particular, we ask whether a given supralinearity mechanism could either introduce a power law behavior when combined with an adaptation model without such behavior, or could destroy a power law behavior in the opposite case.

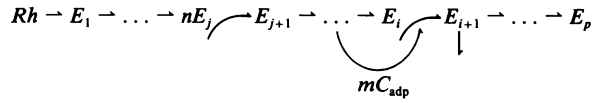
We have studied all the schemes that insert into an otherwise linear chain 1 of the supralinearity mechanisms and 1 of the adaptation mechanisms discussed above (Schemes 2–4). The different cases correspond to different relative positions, along the chain, of the sources and sinks of the two processes; insertion of linear steps among the sources and sinks does not change the functional dependences in the model. By "source" we mean the reaction product in the chain which serves as an accessory material, or proportionally activates an accessory material, intermediating the feedback or feedforward loop. The concentration of the source is assumed not to be influenced by its acting as a source. A "sink" is an enzymatic reaction whose rate is modified by an accessory material. Formally, cooperativity can be considered as a sink without a source.

The models allow two cases for the adaptive mechanism: Negative feedforward, in which the source precedes the sink in the chain; and negative feedback, in which the sink precedes the source. Similarly, there are three cases for the supralinearity mechanism: Positive feedforward, positive feedback, and cooperativity.

In combining these cases, we note that a sink may precede, coincide with, or follow another sink; that two adjacent sources (with no sink between them) are equivalent to a single joint source since their strengths are proportional; and finally that a sink and a source cannot coincide.

With these constraints, 30 distinguishable cases emerge, and it is to these we refer in the following.

We begin by giving, as an example, one of these 30 cases. The example is that shown in Scheme 5, where the supralinear mechanism is cooperativity and precedes the adaptive mechanism, which is a negative feedforward.



Scheme 5

(We will always label the supralinear state j and the adaptive state i. Also, from this point on in this paper, n will be either the number of E_j molecules that must cooperate to accelerate their own activity, or the number of C_{fac} molecules that must bind to E_j to enhance its activity, whereas m denotes the number of binding sites on the E_i molecule which, when fully occupied by C_{adp}, cause the E_i inhibition.)

The final equation that relates R and I for this system follows from the assumption that the input of the adaptive process, $[E_i]$, (Eq. 6) is proportional to the output of the supralinear process, $[E_{j+1}]$, (Eq. 11). The result is

$$R = \frac{F(AI^n + BI)}{1 + G(AI^n + BI)^m}. \tag{17}$$

For very low light intensities, $BI \gg AI^n$ and $1 \gg G(AI^n + BI)^m$, whence R is linear with I. For higher light intensities, the behavior of R with I depends on what happens first: (*1*) AI^n passes BI or (*2*) $G(AI^n + BI)^m$ passes 1. Case *1* implies that the supralinear process expresses itself before the adaptive process as a function of light intensity. For these intensities, the behavior is supralinear before adapting when $G(AI^n + BI)^m$ passes 1. This behavior is shown in the dashed-line curve of Fig. 7 for $m = 1$.

In Case *2*, the adaptive process expresses itself before the supralinear process as a function of light intensity. In this case, for $m = 1$, the response saturates and we have no

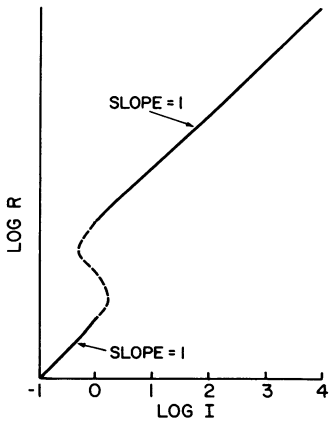


FIGURE 6 The positive-feedback model for supralinearity. As in Fig. 2 but for the mechanism in which an accessory material appears in a feedback manner and enhances the activity of an enzyme. The drawing is schematic and based on Eq. 16. Note that the slope is near 1 until the response reaches some threshold. At this threshold, a discontinuity may occur (see text). From this point on, the response again is proportional to light intensity.

supralinear region, so its behavior is that shown in the solid-line curve of Fig. 7. Note that in any case, the general features of cooperativity and negative feedforward remain in these models, and no new features, such as the appearance of a fractional power law, are created.

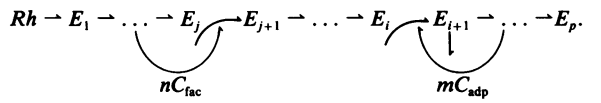
Analysis of the remainder of the 30 combinations of mechanisms enables us to generalize some of the conclusions of this example.

Conclusion *1:* R is linear with I for very low light intensities. This conclusion is valid in general because it is valid for all supralinear and adaptive models, since we have assumed that any cooperativity is not absolute, that is, that the processes are enhanced by, but not dependent on, cooperativity. (However, see comment on "locality" in the Discussion.)

Conclusion *2:* Only models that contain negative feedback as the adaptation mechanism can predict the fractional power law of Eq. 1. From here on we shall therefore concentrate on these models.

Conclusion *3:* The adaptive mechanism must express itself before the supralinear mechanism as a function of light intensity. This is because otherwise the response would have a region of supralinear dependence on intensity in the steady-state response.

A second example will illustrate a further conclusion. Suppose a positive-feedforward process preceding a negative-feedback adaptive process as illustrated in Scheme 6.



Scheme 6

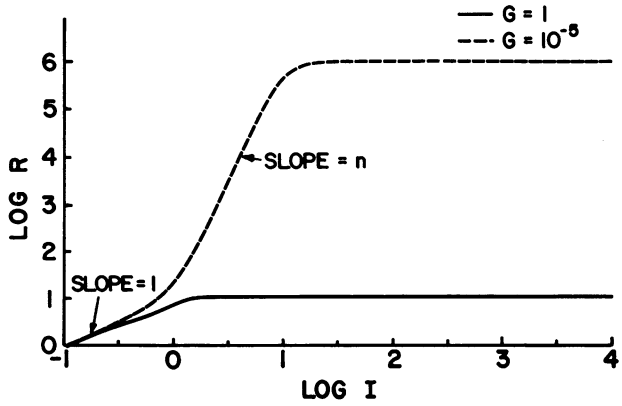


FIGURE 7 The mixed cooperativity and negative-feedforward model for supralinearity and adaptation. As in Fig. 2 but for the model shown in Scheme 5; Eq. 17. The plots are for $m = 1$, $n = 5$, and $A = B = 1$, and F is irrelevant. For $G = 10^{-5}$, the supralinearity expresses itself before the adaptation (*dashed line*). For $G = 1$, the adaptation sets in before the supralinearity (*solid line*). Note that general features of the mechanisms underlying supralinearity and adaptation are present, and no new features are created. This figure also shows that the adaptive mechanism must express itself before the supralinearity mechanism as a function of light intensity, because otherwise there is a supralinear region, as seen in the dashed curve, in disagreement with experiment.

As for Eq. 17, we can calculate the $R - I$ relationship, by using Eqs. 7 and 15. The result is

$$R = \frac{AI + BI^{n+1}}{(F + I^n)(G + R^m)}. \tag{18}$$

The behavior of R in Eq. 18 as a function of I is determined by the behavior of the underlying mechanisms for adaptation and for supralinearity, with the output of the feedforward process serving as the input to the feedback process, i.e., $[E_i]$ is proportional to $[E_{j+1}]$. From Fig. 5, one sees that for low light intensities, $[E_i]$ increases linearly with I. Then, at some intensity $[E_i]$ reaches a break point, $[E_i]_1$, above which it is proportional to I^{n+1}. In Eq. 18, this change of the functional dependence of $[E_i]$ on I happens when the BI^{n+1} term passes the AI term. For even higher intensities, $[E_i]$ reaches a second break point, $[E_i]_2$, above which it becomes proportional to I again. In Eq. 18, this change of behavior corresponds to I^n becoming greater than F.

From Fig. 3, one sees that the adaptation mechanism also has a break point. This is the point at which $[E_i]$ passes the value $[E_i]_0$ at which R changes over from the linear regime to the fractional power regime. In Eq. 18, this occurs when R^m becomes greater than G. From Conclusion 3, adaptation should express itself at intensities that are not larger than those in which supralinearity expresses itself, i.e., $[E_i]_0 \leq [E_i]_1$.

If $[E_i]_0 \ll [E_i]_1$, then the response has a power law regime with $\sigma = 1/(m + 1)$ in the range $[E_i]_0 < [E_i] < [E_i]_1$. However, as the light increases and $[E_i]$ passes $[E_i]_1$, then

$$R = \left(\frac{B}{F}\right)^{1/(m+1)} I^{(n+1)/(m+1)}. \tag{19}$$

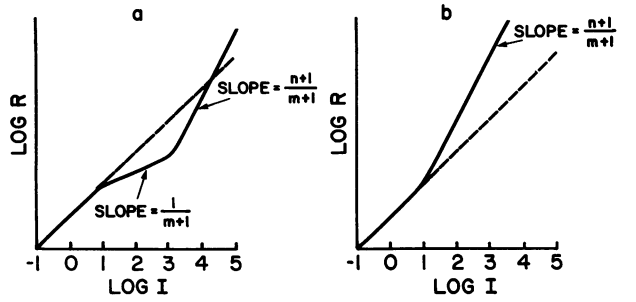


FIGURE 8 The positive-feedforward-preceding-negative-feedback model for adaptation and supralinearity. As in Fig. 2 but for the model shown in Scheme 6; Eq. 18. The number of cofactor molecules that cooperate to accelerate the activity of enzyme E_j is n, and m is the number of binding sites on enzyme E_i that must be occupied by the accessory material that mediates the feedback before the enzyme's inhibition occurs. Slope of 1 is shown for comparison. The parameters of plot *a* were chosen such that the onset of adaptation precedes the onset of supralinearity: $F \gg 10^5$, $A = 10^{15}$, $B = 1$, and $G = 5 \cdot 10^{10}$. Note that after the first fractional power law range, a new obligatory power law regime appears in which the power is increased. The obligatory power law change occurs because the cooperativity that mediates supralinearity precedes the negative feedback in the chain. The parameters of plot *b* were chosen such that the onset of adaptation coincides with the onset of supralinearity: $F \gg 10^5$, $A = 10^5$, $B = 1$, and $G = 10^4$.

In other words, in this case, when the feedforward supralinearity process begins to express itself, the exponent of the power law changes to $\sigma = (n + 1)/(m + 1)$. This change is obligatory because the feedforward depends solely on I, which increases indefinitely. This behavior is seen in Fig. 8 *a*.

Because n must be greater than 1 in order to allow for supralinearity, Eq. 19 states that in this case the slope should change by at least a factor of 2, contrary to experiment.

One must therefore assume that if Eq. 18 is to be valid, the break points $[E_i]_0$ and $[E_i]_1$ must roughly coincide. In this case (Fig. 8 *b*), the response passes from its linear dependence on I directly to the power law regime described by Eq. 19, in agreement with experiment.

Two reservations, however, suggest that schemes like Scheme 6 are unacceptable. The weaker one is that at sufficiently high intensities $[E_i]$ must pass $[E_i]_1$, at which point the supralinear mechanism develops a linear behavior (Fig. 5) and the $R - I$ dependence becomes

$$R = B^{1/(m+1)} I^{1/(m+1)}. \quad (20)$$

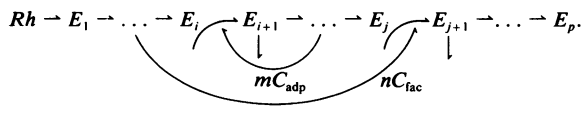
so a change of slope should be seen, and is not. However, this break could occur outside the range of experimental intensities.

The stronger reservation is that to have Eq. 19 match the observed power law, one needs to postulate an unreasonably high value for m, the C_{adp} cooperativity. Since the experimental value for σ is ~0.2, m must be greater than 9 since n must be greater than 1. In fact, the experimental evidence seems to suggest that $n \gg 1$ (Brown and Coles, 1979), which imposes even larger values for m.

We find by inspection of the 30 cases that this result is general.

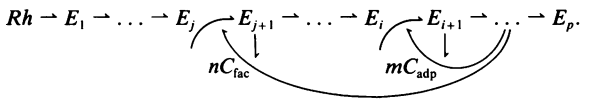
Conclusion *4:* A mechanism in which the source of the accessory material responsible for the supralinearity mechanism precedes in the transduction chain the adaptive process is unlikely, because it must either impose a change in the steady-state power law for some region of light intensity or require too high values for the number of molecules that must cooperate to give rise to adaptation. In the rest of this paper, we shall accordingly assume that the adaptive process must act at a stage of the chain before that which serves as the source of the supralinearity material.

Among the cases that do not satisfy the requirement imposed by Conclusion *4* (that is, the source of the accessory supralinearity material precedes the adaptive process) are those in which a positive feedforward acts after the adaptive stage, but arises before that stage, as shown in the example of Scheme 7 (in Schemes 7 and 8, the adaptation is a negative feedback):



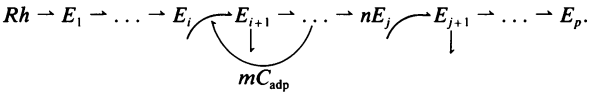
Scheme 7

Cases in which the supralinear process is a positive feedback and acts at a point in the chain before the adaptive process, but with C_{fac} originating after the adaptive process, do satisfy Conclusion 4. An example is Scheme 8:



Scheme 8

A further example of a case that satisfies Conclusion *4*, is Scheme 9:



Scheme 9

Here the supralinearity arises from the cooperativity of n E_j molecules, and the adaptive process is the negative feedback, with C_{adp} coming from a piace in the chain before the supralinear stage. Eqs. 7 and 11 give us the $R - I$ relationship:

$$R = \frac{AI}{F + [E_{i+1}]^m} + \frac{BI^n}{(F + [E_{i+1}]^m)^n},$$

$$E_{i+1} = \frac{GI}{F + [E_{i+1}]^m}. \quad (21)$$

After the linear phase of the $R - I$ relationship, the adaptation occurs, when $[E_{i+1}]^m \gg F$. Because the second term on the right side of the left equation of 21 has a higher power (n), it is negligible compared with the left term for low and intermediate intensities. The response therefore passes over to a power law regime with $\sigma = 1/(m + 1)$.

For higher intensities, the right term has eventually to be taken into account. However, these intensities could be very high, perhaps much higher than the equivalent intensities for which supralinearity is observed in the flash responses. We may explain this as follows: For a flash response, the kinetics of the appearance of C_{adp} could be very slow, yielding a concentration close to zero during the response. The concentration of the material E_j necessary in the cooperativity could be high for relatively low light intensity, and thus make the cooperative process effective. For the steady-state response, on the other hand, the concentration of C_{adp} has time to develop to its maximum. In Eq. 21, C_{adp} is proportional to $[E_{i+1}]$, so that in the steady-state case $AI/(F + [E_{i+1}]^m)$ rises very slowly with I, which postpones to much higher intensities the place where the power n term in the equation becomes non-negligible compared with the linear term. These intensities could even be higher than the intensities at which the response saturates. This behavior is shown in Fig. 9, where the possibility of the high intensity supralinearity is shown schematically by the dotted line.

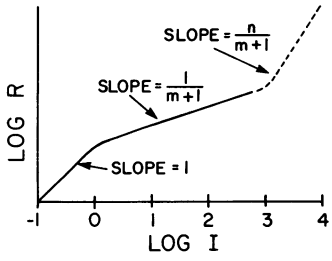
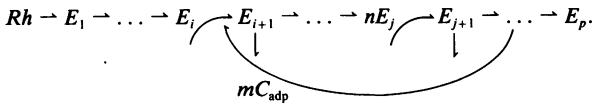


FIGURE 9 The negative-feedback-fully-preceding-the-cooperativity model for adaptation and supralinearity. As in Fig. 2 but for the model shown in Scheme 9, Eq. 21, and the values of Fig. 8 *a* for the constants. Here $[E_{i+1}]$ is the concentration of the product of the enzymatic reaction affected by the feedback. The plot is schematic only, and shows the different power law regions. The dotted line marks a non-obligatory process. That is, after a fractional power law region a new power law region can be established, but might not be, if the feedback lowers the input to the cooperativity stage such that it is below the threshold for cooperativity. The pure power law behavior holds if the cooperativity does not express itself. In this case the model is consistent with experiment (Fig. 1). All the preceding models are not.

In this high intensity $I/(F + [E_{i+1}]^m)$ rises with a power $1/(m + 1)$ of I, and the overall response rises with a power $n/(m + 1)$. We generalize these results in Conclusion 5.

Conclusion *5:* If the adaptive process stage precedes in the transduction chain the source of the accessory supralinearity material and if the source of the accessory adaptive material precedes the supralinearity stage, a power law can be obtained over a wide range of light intensities, because the effects of the supralinearity can be postponed to very high light intensities. In this case, we can say that the mechanism for supralinearity is effectively absent in the steady-state response over the range of light intensities for which the power law is seen. The flash response from a dark-adapted cell can be supralinear with I because of a possible slow kinetics of the adaptive process.

Finally, if the adaptation arises from a negative feedback it could also match the conditions of Conclusion *5*, even if the signal for the adaptive process, C_{adp}, originates at a site after the supralinear stage in the chain. An example of this is shown in Scheme 10, which is similar to Scheme 9 except for the site from which C_{adp} comes:



Scheme 10

In this case, Eq. 21 must be changed to the following form:

$$R = \frac{AI}{F + R^m} + \frac{BI^n}{(F + R^m)^n}. \tag{22}$$

For low and intermediate light intensities, the supralinear term is negligible and thus, after its linear phase, R enters a power law regime with $\sigma = 1/(m + 1)$. For high intensities, Eq. 22 does not behave like Eq. 21. For these intensities $R^m \gg F$ and $B[I/(F + R^m)]^n \gg AI/(F + R^m)$, so one can write

$$R = B^{1/(nm+1)} I^{n/(nm+1)}. \tag{23}$$

This equation represents a power law with $\sigma = n/(nm+1)$. This σ can range from $1/(m + 1)$ (when $n = 1$) to $1/m$ (when $n \to \infty$) so that $1/(m + 1) < \sigma < 1/m$. This result is shown in Fig. 10. This suggests that for such models even if the supralinearity has an influence, it does not change the power law very much. For example, in the *Limulus* ventral photoreceptors, we found $m \approx 4$. In this case, the power law could change from 0.2 to at most 0.25, and probably less, a change that lies within the experimental uncertainties. We generalize this last conclusion.

Conclusion *6*: If the adaptive process precedes in the transduction chain the source of the accessory supralinearity mechanism, and if this adaptive process is a negative feedback with the source of its accessory material at a place later than the supralinear stage, a power law is obtained for a wide range of light intensities. In this case, the supralinearity mechanism can coexist with the adaptation mechanism. Again as in Conclusion *5*, the flash response to a dark-adapted cell can exhibit a supralinear dependence with light intensity, because of a possible slow kinetics of the adaptive process.

DISCUSSION AND SUMMARY

In this paper, we have considered three single-stage mechanisms for explaining light adaptation in photoreceptors.

We have eliminated saturation as a possible mechanism for invertebrate photoreceptor adaptation, on the grounds of its not involving an internal transmitter. Since Bastian and Fain (1979) have provided evidence that light adaptation in toad rods also requires an internal transmitter, the same consideration may apply to vertebrate photoreceptors. Although other observations (Penn and Hagins, 1972; Fain, 1974; Norman and Werblin, 1974; and Kleinschmidt and Dowling, 1975) have been used to suggest a saturative mechanism, Fig. 2 shows that a negative feedforward mechanism may yield a similar behavior. Such a mechanism has been suggested by Tranchina et al. (1984).

The invertebrate power law, however, is consistent only with a negative feedback. According to the model, a

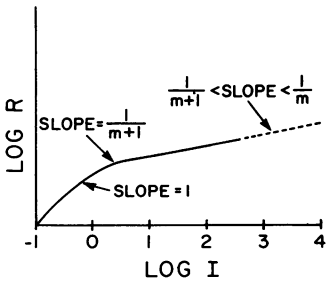


FIGURE 10 The negative-feedback-partially-preceding-the-cooperativity model for adaptation and supralinearity. As in Fig. 2 but for the model shown in Scheme 10, Eq. 22, and the values of Fig. 8 *a* for the constants. The dotted line again marks a non-obligatory process. Note, however, that following a fractional power law region, a new power law region can be established with a slope only a little different from the first. This nearly pure power law behavior holds even if the cooperativity expresses itself. This model too is therefore consistent with experiment (Fig. 1).

material C_{adp} arises from a stage in the transduction chain that is later than the stage it affects, $E_i \rightarrow E_{i+1}$, and it inhibits E_i or activates the removal of E_{i+1} cooperatively: C_{adp} has its optimal effect when it binds to all of its m binding sites in E_i or in the enzyme that removes E_{i+1}. The model predicts a power law with $\sigma = 1/(m + 1)$. Experimentally, the average value of σ was 0.2, which in the model implies $m \approx 4$. Within the model, the kinetics of dark adaptation corresponds to the decay or removal of C_{adp}.

If a mechanism is now added to the transduction chain to explain the supralinear dependence on light intensity of the flash response of dark-adapted cells, this mechanism probably does not precede the place in the transduction chain where the negative feedback acts (see discussion leading to Conclusion *4*). If this requirement is fulfilled, the signal for the negative feedback can still come from a place in the chain either before (Case *1*) or after (Case *2*) the supralinearity mechanism (Scheme 9 and Fig. 9 or Scheme 10 and Fig. 10, respectively). The two cases match the models of Conclusions *5* and *6* of the Theory section, respectively. The difference between these models is that in Case *1*, the supralinearity mechanism is virtually absent in the steady-state response, whereas in Case *2* the supralinearity can in principle coexist with the adaptation mechanism. Using small sinusoidal modulations of a background illumination, Grzywacz (1985) suggested that the supralinearity mechanism does in fact coexist with the adaptation mechanism during the steady-state response. This gives preference to Case *2*.

A light-induced rise in the cytoplasmic concentration of Ca^{2+} is an essential component of the adaptation of *Limulus* ventral photoreceptors (Lisman and Brown, 1972, 1975; Fein and Szuts, 1982). Our results suggest that the Ca^{2+} acts as a negative-feedback transmitter. This in turn implies that the mechanism is not the closing of ionic channels; a mechanism suggested by Kramer and Widmann (1977). This conclusion is further supported by the demonstration that the main source of Ca^{2+} is an intracellular compartment (Lisman, 1976), and that ions that enter through the ionic channels do not release the Ca^{2+} from this intracellular store (Lisman and Strong, 1979).

We suggest that if indeed Ca^{2+} mediates light adaptation, it does so through a reduction in the action of some enzyme. The reaction may be mediated by calmodulin, which appears to be activated by Ca^{2+} in a cooperative manner involving four binding sites (Klee et al., 1980; Means and Dedman, 1980). The cooperativity found by us was indeed close to four.

The models studied here predict an initially linear dependence of the response amplitude on the intensity when the concentration of the different materials is sufficiently low. However, the linear regime may be extended by the slow onset of the adaptational mechanism (Lisman and Brown, 1975; Grzywacz and Hillman, 1985), and by the spatial localization of the adaptation and supralinearity processes near the point of photon absorption, which is discussed below.

Payne and Fein (1986) found that the initial responses to bright flashes can be matched by a model in which light initiates two parallel cascades. One of the cascades is the direct transduction chain to channel opening and the second, which separates from the direct chain before its first amplification stage, creates an agent, probably Ca^{2+}, which accelerates the production rates of several stages of the direct chain in a positive-feedforward manner.

We have previously shown that our flash-response enhancement observations may indeed arise from a positive-feedforward loop (Grzywacz et al., 1987). However, in this paper, we have also shown that adaptation probably arises from a negative-feedback mechanism, and that the source of the facilitating material must follow the point of action of the adaptation.

We suggest accordingly that the Payne–Fein forward-acting Ca^{2+} may well be responsible for the changes in time course of the initial phases of flash responses but cannot be responsible for the bump size modulation seen in facilitation and adaptation.

How general are our conclusions? We have assumed three constraints on our model.

The first constraint is that of a single chain. However, the presence of two parallel interacting chains, such as suggested in the model of Payne and Fein (1986), is formally included in our model as a "feedforward" mechanism.

The second constraint is the assumption that the system is well-stirred, that is, that all concentrations are homogeneous over the relevant part of the cell. Experimentally, this constraint is known to be invalid in general (see Fein and Charlton, 1975*a*, *b*; a review by Hillman, 1983; but a "well-stirred" case reported by Bader et al., 1982). What does this failure imply?

Clearly, any degree of localization of all the component processes implies linearity of the stimulus–response relationship up to the point where the processes induced by separate photons begin to interact. Thus, even in the presence of absolutely cooperative processes (those whose activity is zero when less than two molecules of the cooperative material are present), an initial linear portion of the stimulus–response curve is predicted. However, the requirement of non-absoluteness of cooperativity in this paper, in fact derives from observations on isolated bumps and so cannot be dispensed with. Nevertheless, the stimulus range over which linearity should hold may well be extended by the locality of the processes.

Our most critical constraint is the restriction of our modeling to systems containing only two nonlinear processes, one responsible for light adaptation and the other responsible for response supralinearity. We have not tried to study quantitatively the effects of adding further nonlin-

ear stages, but we make the following comments on such systems which mildly support the idea that there are not many nonlinear stages.

In general, to each nonlinear process in such a system there will correspond an intensity above which the process strongly affects the behavior of the system. Typically, this "break-point" will spread over less than one log unit of intensity, and will separate regions of constant log-log slope (see Figs. 2–10). In any such region, the slope is determined by all the processes that are effective in that region.

In fact, at the intensities studied, the experimental curve exhibits only one breakpoint (Fig. 1). We model this either by assuming that the supralinearity break point is beyond the experimental range of intensities (Fig. 9) or by shaping the model so that the change of slope at the break point is small (Fig. 10). Models in which the supralinearity break point causes a large change in slope cannot be rescued by making the two break points coincide (Fig. 8 *b*), because the value of the observed slope would then require unreasonable values of the adaptive cooperativity. If there are additional nonlinear processes effective in the observed range of intensities, they must either be only mildly nonlinear or their location in the chain with respect to the adaptive and supralinearity processes must be such that no new significant break points in the stimulus–response curve are created (e.g., Fig. 10).

We conclude that our acceptable models may not be unreasonably restrictive.

Finally, we point out that the power law is not a feature unique to invertebrate photoreceptors. Stevens (1970) noted that psychophysical intensity judgment and neural event rate exhibit power law dependences on suprathreshold stimulus intensity for many types of sensory modalities. Cooperative negative feedback could provide the basis for all of these power laws.

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