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# GENERATION AND TRANSFORMATION OF SECOND-ORDER NONLINEARITY IN CATFISH RETINA

Ken-Ichi Naka, Hiroko M. Sakai, Naohiro Ishii

National Institute for Basic Biology, Okazaki 444, Japan

and

Nagoya Institute of Technology, Showaku, Nagaya 466, Japan

*A large part of the response from catfish retinal neurons evoked by a white-noise modulated light stimulus is reconstructed by the linear and the second-order nonlinear components, which shows that the first- and second-order kernels represent the major response characteristics. In catfish retina, amacrine cells are classified as type-C and type-N cells. Type-C cells produce a stable and stereotyped second-order kernel that can be reproduced by squaring an underdamped first-order kernel. This is a linear filter followed by a static nonlinearity and is modeled by a cascade of the Wiener structure. A second-order kernel from the other class of amacrine cells, type-N cells, is reproduced by a simple linear filtering of type-C cell response. This is a static nonlinearity sandwiched between two linear filters and is modelled by a cascade of the Korenberg structure. These findings may greatly simplify future attempts to reconstruct retinal circuitry and may give some insight into the process of complex signal processing in the inner part of the vertebrate retina.*

***Keywords*** — *White-noise analysis, Signal transmission, Vertebrate retina.*

## INTRODUCTION

Vertebrate retinas receive and process an enormous amount of information on the photic environment, which fluctuates continuously in time and space. The output from the retina to the brain, on the other hand, is a series of (discrete) spike trains of less than 0.5 KHz in (carrier) frequency. The amount of information contained in the spike train, therefore, is very limited compared with that contained in visual inputs. To cope with this disparity, the vertebrate retina has evolved two strategies: one is to have a large number of parallel lines or optic nerves and the other is to introduce nonlinearity to compress the amount of information.

Results by Sakuranaga and Naka (16,17,18) showed that the essential features of the responses from catfish retinal neurons evoked by a white-noise modulated light

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Address correspondence to Dr. H.M. Sakai, National Institute for Basic Biology, Okazaki 444, Japan.

could be reconstructed with a reasonable degree of accuracy by the first- to third-order kernels. Sakuranaga and Naka further showed that a large part of the nonlinear response was accounted for by the second-order model rather than by the third-order model (17,18). Although dynamic response of retinal neurons may contain higher-order nonlinearities, the signature of the dynamic responses can be described mostly by first- and second-order kernels.

The vertebrate retina has a class of cells referred to as the amacrine cells. In catfish, the amacrine cells are classified into two classes, type-C and -N cells. Type-C amacrine cells, often referenced as the transient amacrine cells, are found in many lower vertebrate retinas, including mudpuppy (22), goldfish (3,4) and frog (9). A step of light given in the dark produces sharp transient depolarizations both at the onset and offsets of the stimulus. Typical responses from type-C and -N amacrine cells evoked by step modulations of a mean luminance are shown in Fig. 3.

Earlier analyses have shown that responses from type-C amacrine cells are highly nonlinear (11,18) and the mean square errors (MSE) of the linear model (predicted by the first-order kernel) are more than 90%, whereas the second-order model improved the MSE by as much as 60%. Type-N amacrine cells are known as the sustained amacrine cell in other retinas because steps of light given in the dark produce a sustained polarization (4). In catfish, sharp transient depolarizations and oscillations were seen superposed on the steady depolarization (17,2) of type-N cell responses.

In this article we will analyze the second-order nonlinearity produced by amacrine cells in reference to the cascade models. Conclusions drawn are: (1) There is one primordial second-order nonlinearity that is generated by type-C amacrine cells. (2) The nonlinearity is static and the cell response to white-noise input can be synthesized by squaring the output of a differentiating (bandpass) filter. This is a cascade model of Wiener structure in which a linear filter is followed by a static nonlinearity. (3) The second-order nonlinearity observed in amacrine cells of the second type, type-N, can be reproduced by linear filtering of type-C cell responses. This is a cascade model of Korenberg structure. Although we do not have any physiological evidence to show that such filtering and squaring are actually taking place in the catfish retina, these structures are the simplest formal models to account for the modulation responses from the amacrine cells.

## MATERIALS AND METHODS

### Biological

Materials used were the eye-cup preparations of channel catfish, *Ictalurus punctatus*. Experimental and stimulation procedures have been described elsewhere (1,2).

### Data aquisition and analysis

The time course of the white-noise stimulus and resulting cellular responses were initially stored on analog tape (NFR 3000 Data recorder, Sony Corp., Tokyo) and digitized off-line at a rate of 500 Hz and stored in the memory of a VAX 11/780 computer (Digital Equipment Corp., Marlboro, MA). For analysis both the digitized response and the stimulus were filtered (0.1 to 100 Hz) to remove DC components, spurious noise and slow baseline drifts. First- and second-order kernels were computed by crosscorrelating the input, white-noise modulation, $I(t)$, against the output, $V(t)$, as

$$h_1(\tau) = (1/P)\overline{V(t)I(t-\tau)} \ , \tag{1}$$

$$h_2(\tau_1,\tau_2) = (1/2P^2)\overline{V(t)I(t-\tau_1)I(t-\tau_2)} \ , \tag{2}$$

where $h(\tau)$ is the first-order kernel, $h(\tau_1,\tau_2)$ is the second-order kernel and $P$ is the power of stimulus. In a linear system the first-order kernel is the system's impulse response, whereas in a nonlinear system the kernel is the best linear approximation of the impulse response. In the case of light stimulus, the impulse response is produced by a short pulse of light superposed on a mean luminance, $I_0$. Higher-order kernels are produced by the part of the response that is not accounted for by the linear component. Second-order kernels are produced by crosscorrelation between the white-noise input and the part of the response produced by second-order nonlinearity. Therefore the second-order kernel is an indication of the deviation from linear superposition of two responses evoked by two flashes (superposed on a mean luminance, $I_0$) that arrive with an interval of $(\tau_1 - \tau_2)$. Figure 1A shows a typical second-order kernel in a three-dimensional plot (bird's eye view): the kernel has two time axes and the third axis represents the strength of nonlinear interaction. This kernel, similar to the one published by Schetzen (Fig. 13.7-6 in (19)), represents the second-order nonlinearity produced by a square-law device. The three-dimensional structure can be replotted on two dimensions as shown in Fig. 1B. In this plot the peaks and valleys in the three-dimensional plot are shown by contour lines. The positive peaks, depolarizations in neural response, are shown by continuous lines and negative valleys, hyperpolarization in neural response, by dotted lines. The kernel has two time axes for the two inputs (Fig. 1). As the two inputs are interchangeable, the kernel is symmetric around the diagonal. Peaks or valleys on the diagonal are produced by a nonlinear summation of two impulse responses produced by two inputs arriving simultaneously, i.e. $\tau_1 = \tau_2$. We reconstructed first- and second-order models by convoluting a light stimulus, $I(t)$, with a first- or second-order kernel. The accuracy of the model's prediction was indicated by the MSEs between the models and the actual cellular responses. Detailed definitions of terms and computational algorithms and the theoretical treatment of the extension of white-noise analysis to spike trains can be found in Sakuranaga and Naka (16,17,18) and Sakuranaga et al. (15).

## MODELS

A physical or biological system can formally be identified by an analysis of input and output data. One of the techniques available for the identification of nonlinear systems is the cascade approach. Three cascade structures have been studied; the Hammerstein, Wiener and Korenberg structures are shown in Fig. 2. The Korenberg structure is often referred to as the sandwich or LNL structure. The Hammerstein structure is a static nonlinearity followed by a dynamic linear filter, whereas the Weiner structure is a dynamic linear filter followed by a static nonlinearity. In the Korenberg structure, a static nonlinearity is sandwiched between two dynamic linear filters. Victor and Shapley (21) showed that the neuron network leading to the gen-

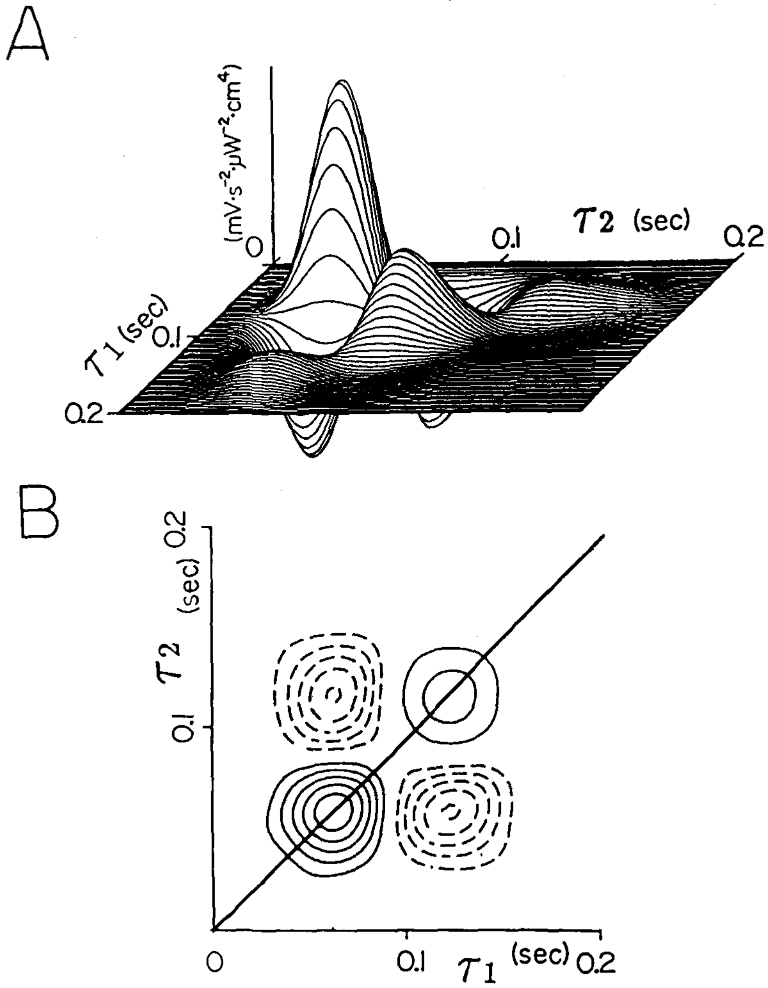

FIGURE 1. A typical second-order kernel displayed in two different ways. (A) Three-dimensional presentation: Cellular depolarizations are by positive peaks and hyperpolarizations by negative valleys. Two time axes and the third amplitude axis are shown. (B) Contour-map representation: Depolarizations are shown by continuous lines and hyperpolarizations by dashed lines. The kernel has a four-eye signature to show that the nonlinearity is the kind produced by a square-law device.

eration of a class of cat retinal ganglion cells, Y-cells, could be modelled by a Korenberg structure or a sandwich model.

The special case of the Wiener structure (23) is a linear filter with a first-order kernel or an impulse response, $g(\tau)$, followed by a squaring device (19,7). The system has the characteristic

$$z(t) = \int_0^\infty g(\tau)x(t-\tau)\mathrm{d}\tau, \tag{3}$$

$$y(t) = z^2(t), \tag{4}$$

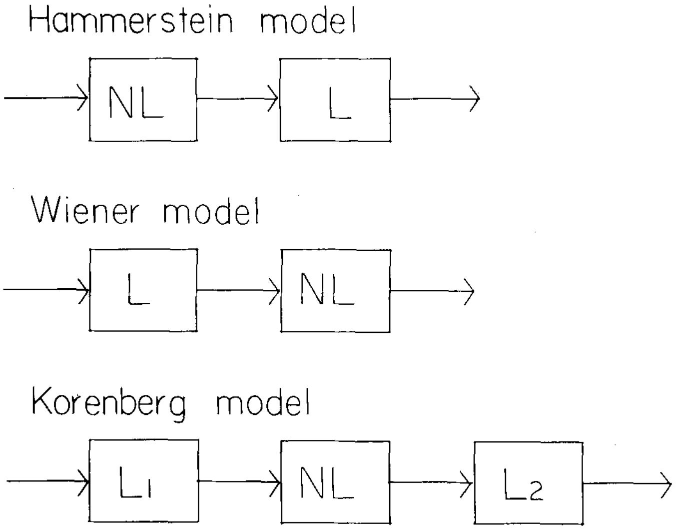

**FIGURE 2. Block diagrams of three cascade models, the Hammerstein, Wiener, and Korenberg structures. L's are linear filters and NL's are static nonlinearity.**

and therefore

$$y(t) = \left[\int_0^\infty g(\tau)x(t-\tau)\mathrm{d}\tau\right]^2$$
$$= \int\int_0^\infty g(\tau_1)g(\tau_2)x(t-\tau_1)x(t-\tau_2)\mathrm{d}\tau_1\mathrm{d}\tau_2. \qquad (5)$$

Thus, the kernels of this system are

$$h_1(\tau) = 0, \qquad (6)$$

$$h_2(\tau_1,\tau_2) = g(\tau_1)g(\tau_2). \qquad (7)$$

This relationship shows that the second-order kernel of this model can be produced by knowing the first-order kernel of the linear filter.

## RESULTS

Power spectra of the responses from type-C and -N amacrine cells evoked by white-noise modulated light stimuli are shown in Fig. 4, together with the spectra of the linear and second-order nonlinear models. The linear model for the type-C cell had a power 20 dB less than that of the cellular responses, but the second-order model predicted the cell responses with a reasonable degree of accuracy, except in the high-frequency region (Fig. 4A). Indeed the MSE for the linear model was 90%, whereas that for the second-order model was 45%. The error in prediction was probably due to the presence of higher-order components in the high-frequency region.

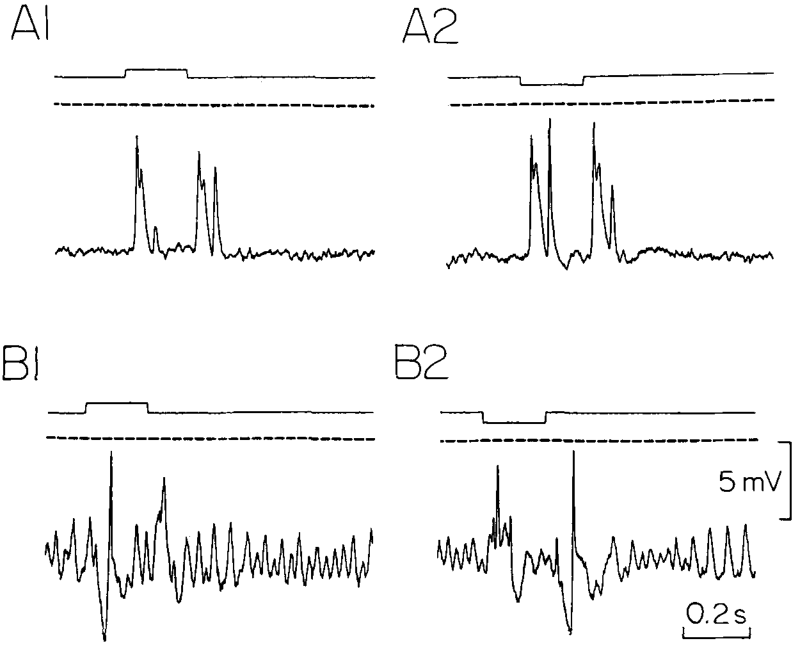

**FIGURE 3.** Responses from type-C (A1,A2) and type-N amacrine cells (B1,B2) evoked either by incremental or decremental steps from a mean luminance. The type-C cell produced similar on-off transient depolarizations at the on- and off-sets of step modulation (A1,A2). The type-N cell produced much more complex responses (B1,B2). Dotted lines indicate dark levels.

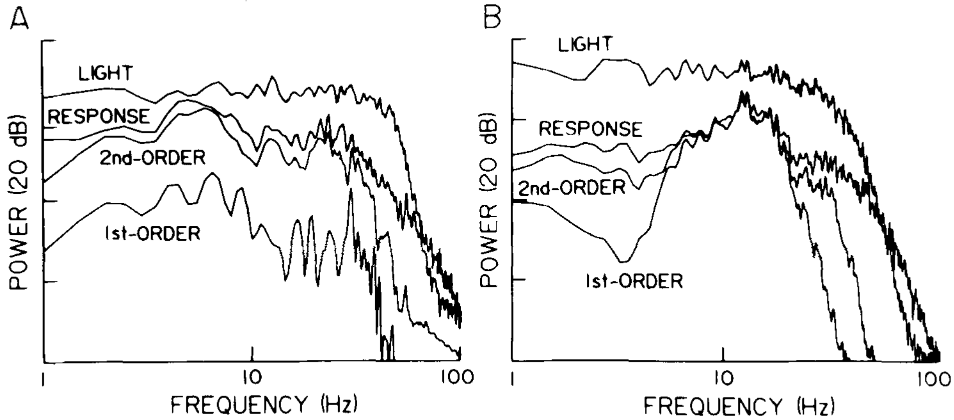

**FIGURE 4.** Power spectra of light inputs, actual responses (marked RESPONSE), linear predictions (marked 1st-ORDER) and prediction by the first- and second-order kernels (marked 2nd ORDER). Spectra in (A) were from a type-C cell and those in (B) were from a type-N cell. Note that type-C cell's response is predicted fairly well by the second-order kernel, except in the high-frequency region. The first-order kernel's prediction was very poor. In the type-N cell, the first- and second-order kernels predicted parts of the cell's response to show that the cell had linear as well as nonlinear components.

For the type-N cell, the linear model predicted cell response quite well for the mid-frequency region around 10 Hz (MSE of 55%), whereas the second-order model improved the model prediction for the lower- and higher-frequency regions (MSE of the second-order model was 35%). As in the case of the type-C cell, the presence of higher-order components was indicated. These results are similar to those reported in earlier papers (17,18) and show that second-order nonlinearity is important in producing dynamic responses in catfish type-C and -N amacrine cells.

Catfish type-C cells produce stable and stereotyped second-order kernels, one example of which is shown in Fig. 5A (18). The kernel has a characteristic configuration (signature) with two on-diagonal positive (depolarizing) peaks and two off-diagonal negative (hyperpolarizing) valleys. The on-diagonal second peak is usually smaller than the first peak. The structure was referred to as the four- or three-eye kernels by Sakuranaga and Naka (18), the latter being the kernels whose on-diagonal second peak was very small. As the kernel is a quadratic function, it is symmetric around the diagonal. The cuts made through the peak and valley parallel to the two time axes (dotted lines in Fig. 5A) produce differentiated (bandpassed) waveforms which are also shown. The waveform of the cuts shown here are similar to that of the impulse response or the first-order kernel from bipolar cells (11,16). The cardi-

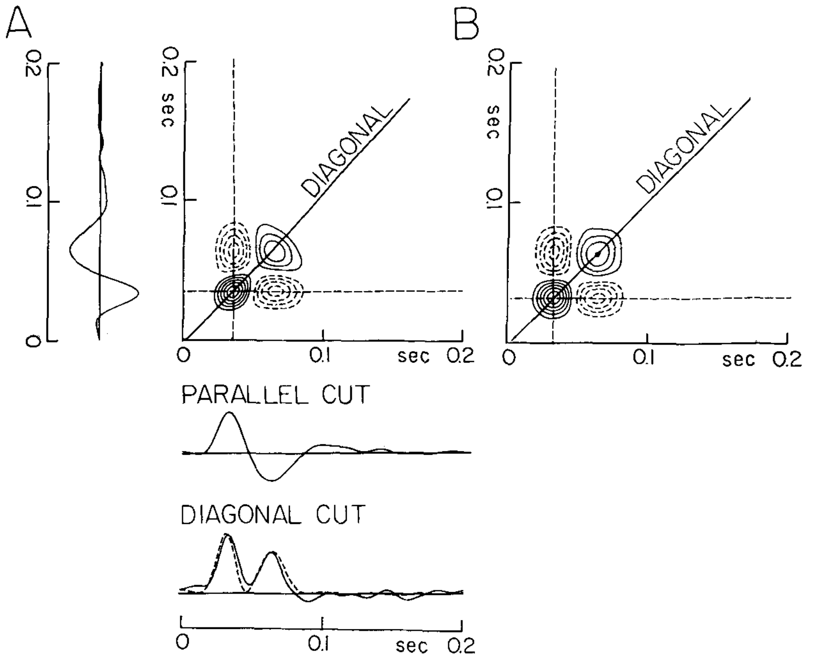

**FIGURE 5.** (A) Actual second-order kernel from catfish type-C amacrine cell with a typical four-eye signature. Cuts are made through the peaks and valleys parallel to the two time axes. Two cuts are shown next to each time axis. The diagonal cut is superposed by the squared product of the cut in dashed line. (B) Second-order kernel produced by a Wiener structure in which the linear filter was the cut shown in (A) and the nonlinearity was a square-law device. Two second-order kernels are very similar.

nal point is that the peaks and valleys of the kernel form a square, the bases of which are parallel to the two time axes. This shows that the kernel can be produced by the squaring of cuts made through the peak and valley. For example, the initial on-diagonal peak is produced by a multiplication of the two initial peaks of the cuts and the off-diagonal valleys by a multiplication of the initial peak of one of the cuts by the negative valley of the other cut (multiplication of the two dimensions). Type-C cell response, therefore, can be reconstructed by squaring a differentiating impulse response.

Mathematically, this operation is represented by

$$h_2(\tau_1,\tau_2) = g(\tau_1)g(\tau_2), \qquad (8)$$

where $g(\tau)$ is the first-order kernel represented by the cut of the second-order kernel shown in Fig. 5A. If $\tau_1 = \tau_2$, then $h_2(\tau_1,\tau_1) = (g(\tau_1))^2$. This shows that the diagonal cut of the second-order kernel is obtained by squaring the cut. As shown in Fig. 5A, this is exactly the case.

Type-C cell response, therefore, can be reproduced by a cascade model of Wiener structure. The kernel shown in Fig. 5B was constructed by squaring the output of a linear filter which was one of the cuts obtained in Fig. 5A. Bipolar cells produce a modulation response that is linearly related to the input modulation, and the cells' impulse response or the first-order kernel is differentiating or underdamped (16). In catfish retina, therefore, the linear dynamic filter is the output of the bipolar cells. In type-C cells, the bipolar cell input is instantly squared to produce the cell's characteristic nonlinear response.

Type-N cells, the other amacrine cell, yield second-order kernels of various configurations that are more complex than the kernels from type-C cells (17,19). Second-order kernels of type-N cells have alternating peaks and valleys elongated perpendicular to the diagonal. Peaks and valleys in kernels from type-N amacrine cells and most ganglion cells do not form a square. Such kernels could not be produced by a simple squaring of bandpassed impulse responses. We have, however, found that almost all second-order kernels from type-N amacrine and ganglion cells are reproduced by linear bandpass filtering performed on the second-order kernel of type-C amacrine cells. Thus, visual inspection of the kernels can lead to immediate predictions with regard to subsequent modeling.

Figure 6 shows the process of reconstruction of a second-order kernel from a type-C second-order kernel. The output of Wiener structure with the second-order kernel shown in Fig. 6A was filtered by a second linear filter, and the filter's output was crosscorrelated against the white-noise input to produce a second-order crosscorrelation shown in Fig. 6B. The reconstructed second-order product (Fig. 6B) is not exactly the same as the actual second-order kernel produced by the type-N cell (Fig. 6C), in the sense that the peaks and valleys are elongated perpendicular to the diagonal. The structure of the second-order kernel produced by type-N cells varies from cell to cell and is not as stereotyped as that produced by type-C cells (5). However, a common feature of type-N second-order kernels is that their alternate peaks and valleys do not form a square as do type-C second-order kernels. We used several different linear filters that may produce a second-order crosscorrelated product identical to the actual type-N second-order kernel, but we have not yet succeeded in finding

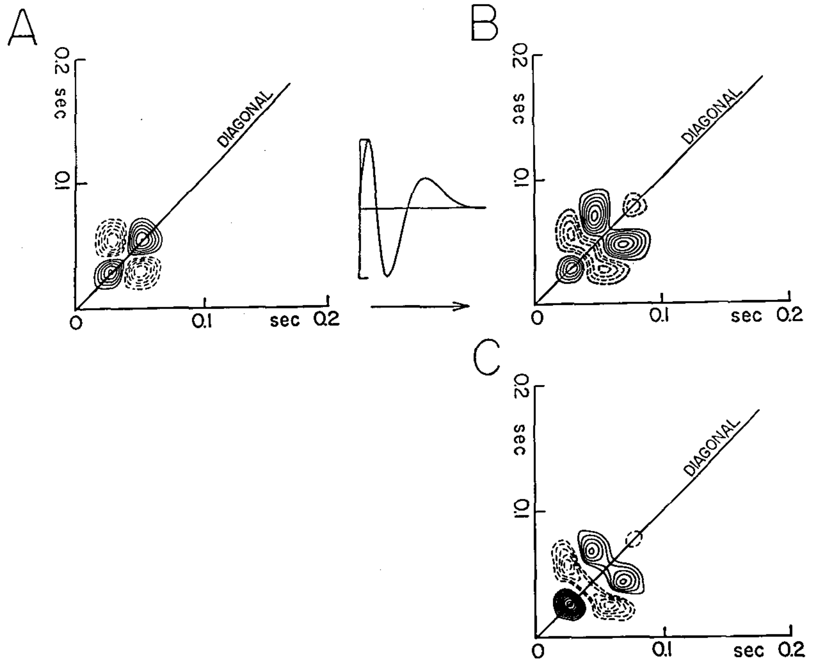

**FIGURE 6. (A) Typical type-C second-order kernel. (B) Second-order kernel produced by a linear filtering of the output of the type-C cell (A). An impulse response of the linear filter is shown. (C) Second-order kernel from catfish type-N cell.**

such linear filters. Quantitative as well as qualitative measurements of the difference between the actual kernel and the reconstructed product have yet to be made.

Thus, we found that the second-order nonlinearity produced by type-N cells and by most ganglion cells can be approximated by the Korenberg structure, in which a static nonlinearity is sandwiched between two linear filters. Various identification schemes for Korenberg structure are described in Korenberg and Hunter (6).

## DISCUSSION

In this study we have shown that second-order nonlinearities produced by two types of amacrine cells, type-C and type-N, can be replaced by cascade models of Wiener and Korenberg structures. These two theoretically derived structures have often been discussed, and it may not be a mere coincidence that these two models are found in catfish amacrine cells. In catfish retina, a large proportion and the signature of dynamic responses of amacrine cells were approximated by first- and second-order Wiener kernels, although higher-order nonlinearities definitely exist in the cells' dynamic response. We have found, however, that these higher-order components account for a much smaller proportion of the modulation response, and that higher-order nonlinearities produce sharp corners and peaks and oscillatory activities (17).

Figure 7 shows a simplified neural circuitry in the catfish inner retinal layer. Cells

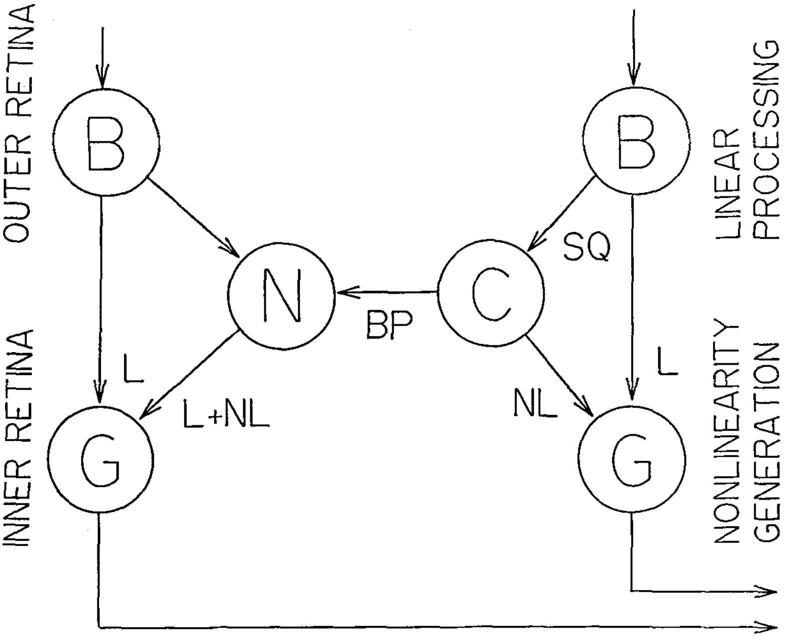

FIGURE 7. Simplified neuron circuitry of catfish inner retina. The modulation responses of bipolar cells (B) are predicted by first-order kernels with a small degree of error. The kernels are differentiated showing the bandpass or underdamped nature of the cell response. Primordial second-order nonlinearity is produced in type-C amacrine cells through a process equivalent to squaring. The output of type-C cells is transmitted to type-N cells through a linear filter. Type-N cells receive their linear components from bipolar cells. Ganglion cells transform analog signals into a series of spike discharges, a point process, which carry results of information transaction within the retina.

in the outer retina, receptors, horizontal cells (2,20–22) and bipolar cells (11,16) respond linearly to input modulation. The bandpassed or underdamped linear responses of bipolar cells are transmitted to ganglion cells. Dynamic responses of type-N amacrine cells contain linear (20–60%) and second-order nonlinear components (15–30% of the total responses) (5). The second-order nonlinearity produced by type-N cells is characteristic of the cell, and the cell's linear response properties, which are represented by the first-order Wiener kernel, resemble those of bipolar cells. Therefore, it is reasonable to assume that the linear signals are directly transmitted from bipolar cells without much modification. Primordial second-order nonlinearity is produced in type-C cells. The nonlinearity is static, and can be replaced by a process equivalent to a squaring of the bandpass or underdamped linear subsystem. In the retina, the underdamped linear subsystem can be found in the dynamic responses of bipolar cells. Thus, the second-order nonlinearity which characterizes the dynamic responses of type-C cells can be described by a cascade of Wiener structure in which a linear subsystem is followed by a static nonlinearity. The output of type-C amacrine cells is fed into type-N amacrine cells through a second bandpass linear filter. The process results in producing the cells' characteristic second-order nonlinearity. The second-order nonlinearity produced by type-N cells can be replaced by a cascade of Korenberg structure. The nonlinearities produced in these amacrine cells are transmitted without much transformation to the ganglion cells. Ganglion cells receive linear signals from bipolar and type-N amacrine cells and second-order nonlinear signals from type-C and -N amacrine cells and generate spikes. Sakuranaga et al. (15) and Sakai and Naka (14) reported that crosscorrelation between the original white-noise input and the spike discharges (transformed into point process) recovers the linear and the second-order nonlinear components. They also found that first- and second-order kernels computed from the spike trains are virtually identical to those from analog responses from bipolar and type-C and -N amacrine cells. The two basic second-order nonlinearities produced in the amacrine cells—one replaced by Wiener structure, the other by Korenberg structure—are transmitted to the brain without much modification.

Victor and Shapely (21) proposed a model for Y ganglion cells in cats, in which a static nonlinearity was sandwiched between two linear filters. They speculated that the first linear filter was the output of the bipolar cells and that the static nonlinearity originated in amacrine cells. This is exactly what we have discussed. Both cat and catfish seem to share a common scheme to generate nonlinearity. The static nonlinearity is a rectification in the cat and a squaring in the catfish. The difference is the presence of higher-order nonlinearities in the cat model and their absence in the catfish model. Cells in the lower vertebrate retinas produce responses similar to those found in catfish retina, and the scheme shown in Fig. 7 may be applicable to other retinas.

There are three major problems to be solved: (a) We have to devise algorithms to estimate higher-order kernels with more accuracy. This will enable us to assess the role of higher-order kernels and also allow us to distinguish between cat and catfish models. (b) We have to devise algorithms so that the second linear filters in the cascade model can be estimated. In this paper the second linear filter was "guessed." (c) We should obtain experimentally the transfer functions among the neurons in the inner retina. This can be done by injecting white-noise signal into one neuron and recording a resulting response from another neuron. By combining the results from these three research areas, we should be able to produce a reasonably well defined circuitry of catfish inner retina.

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