Circuits and Properties of Signal Transmission in the Retina

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This essay looks at the historical significance of three APS classic papers that are freely available online:


Our friend and colleague, Ken-ichi Naka, died on March 5, 2006 as a consequence of a cerebral aneurysm. We review here some of his seminal contributions to our understanding of information processing by the retina. As Matthews (2005) made clear in a recent Classic Essay, our appreciation of how changes in light are coded by the retina took a giant leap forward with Kuffler (1953), who studied the way light-evoked responses of ganglion cells in the cat’s retina depended on the spatial position of the light. He described a center-surround receptive field for ganglion cells. In one type called ON-center, light striking the retinal area over the ganglion cell body increased spike firing, whereas light falling in a concentric peripheral area, the surround, inhibited firing during the light but elicited a burst of spikes at light offset. OFF-center cells had center-surround organization too, but the opposite firing pattern, i.e., centered light inhibited firing whereas peripheral stimulation excited it. A crucial concomitant property was that central and peripheral areas were antagonistic; light falling in one area diminished responses to light striking the other. Consequently ganglion cell responses were dictated not by the absolute light levels, but rather by the difference between central and peripheral illumination.

Kuffler’s measurements raised the question: by which cellular routes do central and peripheral stimuli influence the ganglion cell? This is essentially a question about spatial properties. But as new types of ganglion cells with special coding features (e.g., motion selectivity; Barlow et al., 1964) were discovered, it became clear that the temporal properties of the light stimulus also influenced which retinal circuits were in play.

The overarching goal of Naka’s studies was to provide an analysis of spatiotemporal signal processing in the retina. Over a three-decade period he brought a variety of methods to bear on this task, which encompassed classical morphological and electrophysiological tools such as micropipette recording, current- and dye-injection, pharmacology, Golgi impregnation, immunostaining and electron microscopy. In particular he pioneered the use of dynamic light stimuli, and of Wiener kernels (Wiener 1958) calculated from white noise stimulation, to estimate the degrees of linearity or nonlinearity of particular retinal circuits. To summarize briefly, he and his co-workers found that signal processing in the outer retina, i.e., between photoreceptor, bipolar and horizontal cells, is essentially linear. In the inner retina however, where signals are transmitted between bipolar, amacrine and ganglion cells, substantial non-linearities appear.

In 1962, William Rushton invited Naka to Cambridge University to work on the enigmatic S-potential. Retinal S-potentials (named after their discoverer, Gunnar Svaetichin) were slow potentials recorded with sharp microelectrodes, graded in amplitude according to the intensity of the light stimulus, and either hyperpolarizing or depolarizing, depending on stimulus wavelength and cell type. These responses were so unique to neurophysiological research that for years it was debated whether they had an intracellular origin or were some sort of extracellular field potential. Although a consensus was building that horizontal cells were the source of S-potentials, this question was not definitely settled at the time of the Naka and Rushton studies. But, hedging their bets, they chose to work on a teleostean retina because these characteristically have large horizontal cells.

The major contribution of Naka and Rushton (1967) was to define the spatial properties of the S-potential. They showed that response amplitude fell exponentially as the distance between the recording electrode and light spot increased, even at separations greatly exceeding the dimensions of a single cell. The possibility that light scatter could account for these results was ruled out elegantly by calculating from the intensity-
response relation what could be expected from a scattered stimulus and finding this inconsistent with the measured response. Parenthetically, the intensity response function was shown to resemble closely a Michaelis-Menten function \( R/R_{\text{max}} = I/(I + \sigma) \) where \( R \) is the measured voltage response, \( R_{\text{max}} \) is the saturating response, \( I \) is the light intensity and \( \sigma \) is a half-saturation constant (Naka and Rushton 1966). This generally applicable intensity-response relation for retinal neurons has since been termed a Naka-Rushton function. Their data implied that (a) the bounding layer of the responding element behaved as a leaky membrane, and (b) the responding elements were joined into a functional syncytium much too large to be a single cell. Although the issue of where the recording electrode resided was not resolved in this study, it evoked a memorable statement, which we quote “...whether the space is the interior of one cell (or syncytium) or whether it is cytologically extracellular, but so closely bounded by membranes of surrounding cells that its potential charge is more or less the negative sum of all the charges of its neighbors – a river perhaps, flowing through that crowded community into which all cells can empty their electrical influence. The latter is a rather versatile concept, but degrading. One likes to have one’s electrode in the council chamber, not in the sewer.”

By 1971, the origin of the S-potential as the intracellular response of horizontal cells was established (Werblin and Dowling 1969; Kaneko 1970). At this time Naka was a faculty member in the Division of Biology, California Institute of Technology (Caltech). Naka and Nye (1971) began by mapping receptive fields of catfish (chosen for its ready availability and the large size of many of its retinal neurons) ganglion cells with light spots or concentric annuli of light and described the sort of center-surround receptive fields earlier characterized by Kuffler (1953). Into a space that generated a large S-potential, they injected current while recording simultaneously from a ganglion cell (a technique initiated by Maksimova 1970). The injection sites were later identified as horizontal cells by Procion dye injection. The striking finding was that current which hyperpolarized the horizontal cell (as light did) invariably elicited a response similar to the light-induced surround response from the ganglion cell, and this was true irrespective of whether the ganglion cell was ON-center or OFF-center. In this way Naka and Nye clearly implicated the horizontal cell as being responsible for the ganglion cell surround.

At Caltech, Naka met Panos Marmarelis, then a graduate student with a strong background in Engineering and Cybernetics. They discussed the possibility of using Wiener Kernels to analyze signal transfer between retinal cells and designed a band-pass restricted (0–50 Hz) white noise- modulated command signal that could be used to produce either a fluctuating light signal or a fluctuating current injected into some particular retinal neuron. Kernels of first- or higher-order were generated mathematically. After cross-correlating the temporally modulated light or current stimulus with the membrane voltage response or spike poststimulus histogram, the mean square error between predicted and measured response was estimated and used to determine the degree to which cell responses were matched by the first- (linear) or higher-order (nonlinear) kernels, thus providing a measure of the degree of nonlinearity in the circuit under study.

Marmarelis and Naka (1973) revisited the horizontal cell to ganglion cell circuit studied earlier, but now applying white noise modulation of light intensity, which was confined spatially to either the center (small spot) or the periphery (annulus) of the ganglion cell’s receptive field. Whereas the light stimulus had a relatively flat power spectrum to about 50 Hz, the horizontal’s cell response had a characteristic power spectrum with a corner frequency near 10 Hz; its spectrum was well matched by the first-order kernel, with only a small nonlinear component that became more evident at higher frequencies. Importantly, the horizontal cell system was substantially linear whether a centered spot or an annular light was tested. Thus the horizontal cell system acted as a low-pass filter that measured the DC level induced by the input signal.

Marmarelis and Naka found it easy to match horizontal cell responses with Wiener kernels because of the analog nature of the horizontal cell light-evoked waveform. Ganglion cell spikes were harder to cross correlate because of the jitter in the spike response. Accordingly they averaged multiple responses and generated an instantaneous frequency function (reciprocal of the time interval between adjacent spikes) from the averaged response. In contrast to the horizontal cell, the light to ganglion cell transfer, for either spot or annulus, was fitted less well by a first-order linear model. Addition of a second-order kernel greatly reduced the mean square error, indicating the presence of a strong nonlinearity in the circuit. In this regard, ON-center and OFF-center ganglion cells had very similar characteristics.

The last paper we review (Naka et al., 1975) is one of a series of three directed at identifying the sites and nature of nonlinearity in the retinal circuit. Use of white noise inputs was preceded by morphological (Naka and Carraway 1975) and electrophysiological (Naka and Ohtsuka 1975) examination of individual retinal neurons. For bipolar cells, which receive input from both photoreceptors and horizontal cells, the receptive field organization resembled that of ganglion cells in having opponent center and surround regions, but differed from ganglion cells in that the bipolar cells respond to light with analog voltages rather than spike trains. White noise analysis revealed that the transfer functions of bipolar cells, like those of horizontal cells, were well fitted by the first-order kernel, whether centered or annular light stimuli were used to stimulate the cell. With this finding, Naka and co-workers established that signal processing in the outer retina was substantially linear. Essentially the bipolar cell compares two signals: one local, emanating from the spot at the center of the receptive field, and a second integrating stimulus from the surround. The bipolar cell output is a difference signal representing the contrast between center and surround. Thus Kuffler’s (1953) finding for ganglion cells also is encountered in the outer retina and transmitted to the inner retina by bipolar cell axons.

In the inner retina, bipolar cell axons drive amacrine and ganglion cells. Amacrine cells are a very diverse class of retinal neuron, some of which respond to light increments with rapidly activating and inactivating transient voltages, others with sustained voltages that turned on and off more slowly. In probing these neurons with white noise inputs, Naka found that the functions of sustained subtypes also were fitted by first-order kernels, whereas those of transient cells were markedly nonlinear. These data point to a fundamental dichotomy in retinal signal processing within the inner retina. The linear retinal circuit preserves the DC level signal and can account for the center-surround organization of certain ganglion cells de-
scribed by Kuffler. In essence the DC signal (center ± surround) dictates the sign and magnitude of the postsynaptic potential and thereby alters spike firing. This circuit is ideal for signaling contrast and has been shown to participate also in color coding. The nonlinear circuit ignores the DC signal, instead concentrating on transient shifts in membrane potential that are optimized for signaling dynamic inputs such as stimulus motion and direction of motion.

Naka’s investigations heralded the start of a new era in understanding how information about light stimuli is processed by the retina. The first phase consisted of developing the techniques for recording from small cells, including most retinal neurons, then classifying the cell’s light evoked response and finally identifying the cell with dye injection. During this phase most researchers utilized brief steps of light from darkness for functional characterization. But more recent studies (e.g., Chichilnisky 2001; Hosoya et al., 2005) take into account that daytime vision consists primarily of distinguishing objects whose position and luminance vary (the visual scene) superimposed on a mean luminance (a function of the level of daylight illumination). Thus a more physiological light stimulus presents a wide range of modulations about a mean value, precisely the sort of stimulus provided by white noise. This was Ken-ichi Naka’s great insight. His pioneering research showed how white noise modulated stimuli characterized the dynamics of retinal neuronal responses in ways that were experimentally feasible and appropriate for assessing their role in creating a retinal code for vision (reviewed in Meister and Berry 1999).

REFERENCES


