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A high frequency resonance in the responses of retinal ganglion cells to rapidly modulated stimuli: A computer model

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Abstract

Brisk Y-type ganglion cells in the cat retina exhibit a high frequency resonance (HFR) in their responses to large, rapidly modulated stimuli. We used a computer model to test whether negative feedback mediated by axon-bearing amacrine cells onto ganglion cells could account for the experimentally observed properties of HFRs. Temporal modulation transfer functions (tMTFs) recorded from model ganglion cells exhibited HFR peaks whose amplitude, width, and locations were qualitatively consistent with experimental data. Moreover, the wide spatial distribution of axon-mediated feedback accounted for the observed increase in HFR amplitude with stimulus size. Model phase plots were qualitatively similar to those recorded from Y ganglion cells, including an anomalous phase advance that in our model coincided with the amplification of low-order harmonics that overlapped the HFR peak. When axon-mediated feedback in the model was directed primarily to bipolar cells, whose synaptic output was graded, or else when the model was replaced with a simple cascade of linear filters, it was possible to produce large HFR peaks but the region of anomalous phase advance was always eliminated, suggesting the critical involvement of strongly non-linear feedback loops. To investigate whether HFRs might contribute to visual processing, we simulated high frequency ocular tremor by rapidly modulating a naturalistic image. Visual signals riding on top of the imposed jitter conveyed an enhanced representation of large objects. We conclude that by amplifying responses to ocular tremor, HFRs may selectively enhance the processing of large image features.

Keywords

Cat; Alpha ganglion cell; Y ganglion cell; Amacrine cell; Gap junction; Simulation

Introduction

A standard measure of a retinal ganglion cell's responsiveness to time varying stimuli is the temporal modulation transfer function (tMTF), which plots the amplitude of the sinusoidal variations in the average firing rate as a function of stimulus frequency. In a number of studies, the tMTFs recorded from brisk ganglion cells in the cat retina revealed only a single

broad peak centered around 10 Hz (Shapley & Victor, 1978; Victor & Shapley, 1979; Shapley & Victor, 1981). However, subsequent experiments, which probed responses across an expanded range of stimulus frequencies, reported a quite unexpected feature in ganglion cell tMTFs, namely, a prominent high frequency resonance (HFR) between 60–70 Hz (Frishman et al., 1987). While the responses to temporally modulated stimuli are often complex (Reich et al., 1997), the band-pass character of ganglion cell tMTFs below approximately 40 Hz can be largely explained by a combination of known mechanisms. Adaptation, present at all stages of retinal processing (Frishman & Sieving, 1995; Shapley, 1997; Fahey & Burkhardt, 2001; Hurley, 2002), will suppress ganglion cell responses to slowly varying stimuli. Likewise, responses to rapidly varying stimuli will be suppressed by a variety of low-pass filtering mechanisms, including the finite time constants of retinal neurons (O'Brien et al., 2002) as well as the finite duration of the phototransduction process (Schnapf et al., 1990). Responses to sinusoidally injected currents also peak around 10 Hz (Robinson & Chalupa, 1997), suggesting that intrinsic membrane properties of brisk cat ganglion cells may also contribute to their band-pass behavior at moderate temporal frequencies. In comparison, the mechanisms responsible for HFRs are unknown.

There are numerous feedback processes in the retina, at both the cellular and synaptic levels, that could in principle produce a large resonance response. However, the HFRs seen in cat Y ganglion cells exhibit certain characteristics that suggest wide-field amacrine cells, especially those possessing very large effective dendritic and/or axonal radii, are likely to be involved. In the cat retina, the HFRs evoked by diffuse temporally modulated stimuli are approximately twice as large as those elicited by gratings of optimal spatial frequency (Frishman et al., 1987), implying that the underlying mechanisms extend well into the Y ganglion cell surround. Moreover, the corresponding phase response curves recorded from cat Y retinal ganglion cells exhibit a prominent kink, or abrupt phase advance, at frequencies around 30–40 Hz, a region where low-order harmonics of the sinusoidal stimulus overlap the HFR peak. Horizontal cells are thought to contribute to ganglion cell surrounds and might be hypothesized to underlie HFRs via negative feedback on to cone pedicles (Frishman et al., 1987; Smith, 1995). However, the resonance in horizontal cell tMTFs is much smaller and occurs at lower temporal frequencies than the HFRs measured in cat Y ganglion cells (Foerster et al., 1977). In addition, the phase response curves recorded from cat horizontal cells do not exhibit an abrupt phase advance over the appropriate range of stimulus frequencies. Alternatively, anatomical studies have identified a class of axon-bearing amacrine cells in the cat retina that appear well suited to mediate HFRs in Y ganglion cells. These amacrine cells are tracer coupled to alpha ganglion cells and give rise to long axons that can extend several millimeters (Vaney, 1994). The processes of axon-bearing amacrine cells contact bipolar, amacrine, and ganglion cells, including alpha cells (Kolb & Nelson, 1993; Freed et al., 1996), potentially forming a resonance circuit that might account for the experimentally observed properties of HFRs.

Here, we used a computer model to investigate whether inhibitory feedback from spiking, axon-bearing amacrine cells could reproduce the main properties of experimentally recorded HFRs in cat Y ganglion cells in a manner consistent with retinal anatomy and physiology. We also considered an alternative, yet still biologically plausible, mechanism by which wide-field amacrine cells might contribute to HFRs, namely, axon-mediated feedback onto bipolar cell terminals (Euler & Wässle, 1998; Euler & Masland, 2000; Freed et al., 2003; Shields & Lukasiewicz, 2003). Finally, we examined to what extent a simple linear model, consisting of cascaded band-pass filters in series with a harmonic oscillator, could reproduce the experimentally observed properties of HFRs, regardless of other physiological or anatomical considerations. Whereas all three of the earlier mentioned models could qualitatively account for the principal features of the experimentally measured tMTF, including a sharp resonance at the appropriate frequency, only axon-mediated feedback from

spiking amacrine cells directly onto ganglion cells could account for the anomalous advance in the corresponding phase plots. Because other possible physiological mechanisms involving wide-field amacrine cells were not considered, including intrinsic membrane properties (Soleissio et al., 2002; Vigh et al., 2003) and repetitive firing (Troy et al., 1995), the present model must be regarded as incomplete. Nonetheless, our results suggest that only a strongly non-linear circuit, as represented here by a negative feedback loop consisting of axon-bearing amacrine cells that are both electrically-coupled with, and provide strong inhibition to, ganglion cells, can account for the amplitude, shape, location and size-dependence of HFR peaks recorded from cat Y ganglion cells as well as for the abrupt advance in the corresponding phase response curves.

Finally, the model was used to investigate whether HFRs might directly contribute to the processing of visual stimuli. The frequency spectrum of ocular tremor, an ongoing small amplitude jitter, that is a ubiquitous component of normal eye movements (Martinez-Conde et al., 2004), overlaps the range of frequencies characteristic of HFRs. Could ocular tremor interact with HFRs to transmit additional visual information to the brain? We simulated ocular tremor by adding to a naturalistic input image a temporal modulation whose central frequency was near the HFR peak, consistent with the frequency of ocular tremor in primates. Our results suggest that ocular tremor improves the transmission of visual information around the jitter frequency without corrupting rate-coded information. Consistent with the increased resonance response evoked by diffuse stimuli, we conclude that ocular tremor may be coupled, via HFRs, to a distinct retinal information channel that utilizes high frequency temporal coding to inform the brain about large image features.

Materials and methods

Model overview

The model retina consisted of five parallel two-dimensional grids, one for each of the following five distinct cell types: bipolar cells (BPs), small amacrine cells (SAs), large amacrine cells (LAs), poly-axonal amacrine cells (PAs), and alpha ganglion cells (GCs). The BP, SA, and PA grids were denser than the LA and GC grids as the corresponding cell types were smaller. The interconnections between these five cell types could be organized conceptually as follows (Figs. 1A, 1B). The BPs were activated directly by the external stimulus, representing their input from cone photoreceptor terminals, and in turn produced excitatory postsynaptic potentials (EPSPs) in both ganglion cells and amacrine cells according to a random process (Freed, 2000). EPSPs were balanced by inhibitory postsynaptic potentials, or IPSPs, from the three different amacrine cell types, which encompassed 3 different spatial scales: (1) SAs whose dendritic fields were the same size as those of the bipolar cells, (2) LAs whose dendritic fields were the same size as those of the ganglion cells, and (3) PAs whose dendritic fields were the same size as those of the bipolar cells, but whose axonal connections spread out over a large area. Of the three amacrine cell types in the model, only the axon-bearing amacrine cells fired spikes. All three amacrine cell types made feedforward synapses onto ganglion cells, feedback synapses onto bipolar cells, as well as serial synapses among themselves. The serial interactions between the different amacrine cell types formed a negative feedback loop that increased the dynamic range of the model retina by helping to prevent the responses of any given amacrine cell type from becoming disproportionately large. The axon-bearing amacrine cells were excited primarily via their local gap junctions with neighboring ganglion cells and gave rise, in turn, to long-range inhibition that represented the essential feedback mechanism responsible for HFRs in the retinal model. The behavior of the model in response to a variety of stimuli, the robustness of the model with respect to both numerical and physiological parameters, and the connection of the model to anatomical and electrophysiological data, are described in detail elsewhere (Kenyon & Marshak, 1998; Kenyon et al., 2003, 2004a, 2004b, 2004c).

Some model parameters were modified from previously published values. Specifically, all axon mediated feedback interactions were assigned a fixed synaptic delay of 2 ms and a finite transmission delay, corresponding to an action potential conduction velocity of four ganglion cells per time step (~ 1 mm/ms), was incorporated. The time constant of the axon bearing amacrine cells was also increased slightly, from 5 to 7.5 ms. By increasing the overall delay of the axon-mediated negative feedback loop, the above changes tended to increase HFR amplitudes, but this effect was compensated for by reducing the strength of the feedback inhibition onto the model ganglion cells by a factor of 0.44. Overall, the earlier mentioned changes made little qualitative difference in the behavior of the dynamic feedback circuit but provided a better fit to the HFRs recorded from cat Y ganglion cells.

Stimuli

The model retina was stimulated by temporally modulated spots of varying size. Spot stimuli were used instead of gratings because these allowed us to conveniently pool over many ganglion cells, thereby improving the signal-to-noise ratio of the measured responses. Given computational constraints, it was not feasible to reproduce the long recording times used in physiological experiments but this limitation was overcome by simultaneously recording from many ganglion cells in parallel. In all experiments, the modulation amplitude, defined as $(\text{peak} - \text{trough})/(\text{peak} + \text{trough})$, was equal to 0.5, unless otherwise noted. The maximum intensity for all temporally modulated stimuli was set to 0.75 and the minimum intensity to 0.25, resulting in a time-averaged intensity of 0.5. To further increase the number of stimulated cells available for pooling, multiple spots were typically presented on the same run. To ensure that the interactions between spots were negligible, the density of spots was kept low—in no case did presenting multiple spots cause more than 1016th of the total retinal area to be stimulated. In test cases we verified that equivalent results were obtained when only a single spot stimulus was applied. For spot sizes covering 1×1 , 2×2 , and 4×4 ganglion cells, 64 separate stimuli were applied during each run, whereas 16 separate stimuli were applied for the 8×8 spot. In order to approximate the dynamics of the outer retina, which was not explicitly modeled, a temporal low pass filter with a time constant of 10 ms was applied to all stimuli. Unless otherwise noted, all tMTFs were obtained using a standard spot stimulus, consisting of a uniform square covering a 4×4 array of ganglion cells.

To investigate the potential contribution of HFRs to amplifying the responses to ocular tremor, we modulated a naturalistic image at 72 Hz, such that the mean amplitude of the brightest pixel was 0.5 and varied between 0.25 and 0.75, exclusive of added noise. Because the retinal model was not designed to respond to very small spatial displacements, such as are typically produced by ocular tremor, a direct temporal modulation was used as a surrogate. Image modulations were either purely sinusoidal, or else contained varying amounts of spectral noise to more closely simulate ocular tremor. Spectral noise was incorporated by adding additional Fourier components whose phases were chosen randomly over the interval $0-2\pi$ and whose amplitudes fell off with distance from the central modulation frequency according to a Gaussian function of the indicated width.

Data analysis

All tMTFs were constructed as follows. Multi-unit peri-stimulus-time-histograms (mPSTHs) were constructed by binning spikes from all ganglion cells activated by the same spot stimulus. The simulation was allowed to run without stimulation for 200 ms to eliminate startup artifacts. To allow a quasi-stationary state to be reached, temporally modulated stimuli were applied for 800 ms before recording data for analysis. Data were always collected for 1 s, regardless of stimulus frequency. Multi-unit spike trains recorded from separate spots were treated as independent stimulus trials. Data were binned using a time

unit of 1 ms. The mPSTHs for each temporal modulation frequency were Fourier transformed to determine the magnitude and phase of the fundamental component. Multi-unit tMTFs were constructed by plotting the magnitude of the fundamental Fourier component as a function of the temporal modulation frequency, scaled by the stimulus contrast. Multi-unit phase response curves were similarly obtained by plotting the phase of the fundamental Fourier component on the same abscissa. Because the phase could only be determined modulo 360° , smoothness criteria were employed to obtain maximum continuity in the phase plot. To quantify the amplitude, shape and location of the HFR peak, tMTFs were fit empirically using the sum of a Gaussian, to match the low frequency portion of the curve, plus a Lorentzian, to account for the high frequency resonance, with the free parameters determined using a Levenberg-Marquardt search algorithm (Press et al., 1986), implemented in Matlab.

For reconstructing naturalistic images, we collected data from 200–7700 ms following stimulus onset. Retinal output was divided into 2×2 arrays of neighboring ganglion cells. Long reconstruction times were used to mitigate signal-to-noise issues arising finite data. A measure of the information conveyed by the mean firing rate was estimated by first setting the intensity of each in the reconstructed image equal to the total number of spikes occurring in the corresponding 2×2 array of neighboring glion cells over the recording interval. Information conveyed the high frequency temporal modulations was displayed by putting the power spectra from the multiunit spike trains consisting of 2×2 arrays of neighboring ganglion cells. For static and purely sinusoidally modulated images, the intensity of each pixel in reconstructed image was initially set equal to the peak spectral amplitude (the square root of the corresponding peak in the power spectrum) between 60–80 Hz, whereas for temporal modulations that included a finite spectral spread, the average amplitude between 60 and 80 Hz was used. A final rescaling was performed both the rate-and temporally-reconstructed images so that had zero mean and an average contrast of one.

Linear model

A linear model, containing a cascade of band pass filters connected in series with a harmonic oscillator, was used as an alternative method for reproducing the major features of the tMTF recorded experimentally from cat Y ganglion cells (Fig. 1C). The frequency portion of the tMTF, below approximately 40 Hz, modeled using a combination of feed forward and feedback inhibition whose parameters were determined empirically using Levenberg-Marquardt search algorithm (Press et al., 1986) to obtain the best fit to the tMTF generated by the retinal model.

The transfer function for the band pass filter representing forward inhibition was given by

$$G_{FF}(\omega) = \frac{i\omega\tau_s + 1 - R_{FF}}{-\omega^2\tau_s\tau_l + i\omega(\tau_s + \tau_l) + 1}, \quad (1)$$

with $\tau_s = 8.3$ ms, $\tau_l = 10.0$ ms and $R_{FF} = 1.0 - 0.0045$.

The transfer function for the band pass filter representing feedback inhibition was given by

$$\gamma_{\pm} = \frac{1}{\tau} (1 \pm iR_{FB}), \quad (2)$$

$$G_{FB}(\omega) = \frac{1}{2} \left(\frac{1}{(\gamma_- + i\omega)} - \frac{1}{(\gamma_+ + i\omega)} \right), \quad (3)$$

with $\tau = 17.2$ ms and $R_{FB} = 1.0$ (R_{FB} was fixed).

An intrinsic, damped harmonic oscillator was used to model the HFR, whose transfer function was given by

$$\alpha = \sqrt{\omega_0^2 + \beta^2}, \quad (4)$$

$$G_{HO}(\omega) = \frac{1}{2\pi} \left[\frac{1}{\omega + (\alpha + i\beta)} - \frac{1}{\omega - (\alpha + i\beta)} \right], \quad (5)$$

with $\omega_0 = 2\pi \cdot 75.88$ and $\beta = 0.091\omega_0$, setting the central frequency of the harmonic oscillator and the degree of damping, respectively.

The total transfer function was given by the product of the above three terms, normalized so that the maximum responsivity between 0 and 30 Hz was 77.41.

Results

Responses to time-varying stimuli

Representative multi-unit peri-stimulus-time-histograms (mPSTHs) recorded in response to large sinusoidally varying spots, each covering a 4×4 array of model ganglion cells, were plotted for a range of stimulus frequencies, from 5 Hz to 93 Hz (Fig. 2, black lines). The most obvious feature across the range of stimulus frequencies examined was the strong periodic modulation produced by 15 Hz time-varying stimulation. As measured by the peak-to-trough amplitude in the mPSTH, constructed from multi-unit spike trains that included all 16 ganglion cells activated by the spot, the response to 15 Hz stimulation was substantially larger than to either the 5 Hz or 46 Hz stimulus. Across all stimulus frequencies tested, the mean firing rate remained nearly constant at 79 ± 5 Hz, compared to a background rate of 31 Hz, which is well within the range of observed resting firing rates for Y ganglion cells in the cat retina (Passaglia et al., 2001). Raster plots of single-unit spike trains recorded from 8 model ganglion cells (dark gray ticks) and 8 axon-bearing amacrine cells (light gray ticks) are shown superimposed on the mPSTHs. For these two cell types, which were the only spiking neuron types implemented in the model, strong periodic clustering was evident in the responses to 15 Hz modulation but not in response to 5 Hz or 46 Hz modulation, in agreement with the relative amplitudes of the corresponding mPSTHs. Whereas the responses of brisk cat ganglion cells to low and moderate temporal frequencies reflect a variety of factors, the steady decline in the response amplitudes of the model ganglion cells to stimulus frequencies below 10 Hz was due entirely to a combination of feedforward and feedback inhibition, because no explicit adaptation mechanisms or voltage-gated currents were implemented.

Model ganglion cells also exhibited elevated responses to 73 Hz stimulation, which were considerably larger than the responses elicited by either 46 Hz or 93 Hz stimulation (Fig. 2), reminiscent of a high frequency resonance (HFR) observed in cat Y ganglion cells in response by diffuse, rapidly varying stimuli (Frishman et al., 1987). Visual evidence of periodic clustering in the underlying spike rasters was not as apparent at these elevated stimulus frequencies, but such temporal patterning would likely have been masked by the crowding of successive stimulus cycles. To correct for this bias, spike rasters were replotted using a variable time scale corresponding to a fixed number of cycles of the applied stimulus (Fig. 3, left column). To compensate for the expanded time scale, the number of cells displayed in each raster was increased so that the raster plot corresponding to 5 Hz

stimulation contained two model ganglion cells, that for 15 Hz stimulation contained six ganglion cells, and so forth, up to a maximum of 64 (note that for stimulus frequencies above 15 Hz, successive rows in the raster plots overlapped). At this expanded time scale, the relative increase in periodic clustering in response to 73 Hz stimulation, compared to 46 Hz or 93 Hz stimulation was more apparent. In addition, it can be seen that the timing of spikes across the population of axon-bearing amacrine cells was similar to those generated by the model ganglion cells, although the average firing rate was somewhat lower.

To further quantify model ganglion cell responses to time varying stimuli, each mPSTH was Fourier transformed and the fundamental frequency component overlaid on the corresponding spike rasters (Fig. 3, left column, solid black lines). The amplitude and phase of the fundamental Fourier components were well matched to the degree of periodic structure evident in the associated raster plots. As for cat Y ganglion cells (Frishman et al., 1987), periodic modulations in the firing rates of the model ganglion cells were evident even at stimulus frequencies above 90 Hz, here corresponding to peak-to-trough variations of almost 50 impulses per second.

As a means of summarizing the responses across the full range of stimulus frequencies tested, the phases and amplitudes of each fundamental Fourier component, for time-varying stimuli between 1 Hz to 100 Hz, were overlaid using a constant vertical offset and plotted relative to the phase of the sinusoidally varying input (Fig. 3, right column). Ganglion cell responses were clearly elevated over two distinct frequency bands, one centered around 15 Hz and another around 73 Hz. In general, the response phase of the model ganglion cells lagged progressively with increasing stimulus frequency, except for a region where the response phase remained constant or even advanced slightly, between 30–40 Hz.

To more precisely quantify the responses of the model ganglion cells to temporally modulated stimuli, the amplitudes and phases of the fundamental Fourier components were plotted separately as a function of stimulus frequency (Fig. 4a and 4b, respectively), with the Fourier amplitude scaled by the stimulus contrast ($= 0.5$) to yield a multi-unit tMTF whose vertical axis was expressed in units of responsivity (ips/percent contrast). Corresponding values obtained from cat Y ganglion cells, re-plotted from Frishman et al. (1987), are shown for comparison (Figs. 4c and 4d, respectively).

In both the cat and model data, the HFR peaks in the corresponding tMTFs were very prominent. A combination of Gaussian and Lorentzian functions (Figs. 4a, 4c, solid lines) were used to fit the tMTF data (Figs. 4a and 4c, circles, only one-quarter of the model-generated data points were plotted), with the Lorentzian used to quantify the amplitude, frequency and width of the HFR peak and a Gaussian function used to account for the broad low frequency response. Although the shapes of the tMTFs were qualitatively similar, the responsivity values for the model were approximately a factor of 10 less than those measured experimentally, indicating that the cat retina is much more sensitive to small changes in contrast than were our simulations. Given the intrinsic level of noise in our model, it was not possible to reproduce the exquisite contrast sensitivity of brisk cat ganglion cells while maintaining adequate dynamic range. In addition, the HFR peak in the cat data, relative to the low frequency resonance around 10 Hz, was proportionately smaller than the HFR peak obtained from the retinal model. Methodological differences may have amplified HFRs in our analysis, particularly the use of multi-unit recordings and the use of smaller 1-ms time bins that could better resolve high frequency structure.

The phase response curve obtained from the retinal model was also qualitatively similar to that recorded from cat Y cells (Figs. 4b and 4d, respectively). Solid lines were not parametric fits as with the tMTFs but simply connected neighboring points (again, only one-

quarter of the model-generated data points were plotted). In both sets of data, responses at temporal modulation frequencies below 10 Hz were phase advanced relative to the stimulus. A phase advance of 90° is consistent with the transient character of Y ganglion cell light responses, which thus achieve maximum activation when the intensity is increasing most rapidly. At very low temporal frequencies, below 2 Hz, model ganglion cell responses moved back into phase with the stimulus, a behavior that was not exhibited by cat Y ganglion cells. This discrepancy may be caused by the absence of a cone-based mechanism for light adaptation in the model that would have further reduced responses to slowly varying stimuli. As the temporal modulation frequency was increased above 2 Hz, the response phase of the model ganglion cells became progressively more lagged, reflecting a fixed activation latency of approximately 10 ms. In cat Y cells, phase lags accumulated more steeply over a similar range of temporal frequencies, a discrepancy that may be accounted for by the absence of known fixed delays in the model, such as those caused by photo-transduction (Schnapf et al., 1990). The trend towards increasing phase lag was interrupted by an inflection, or kink, which in the experimental and model data occurred at approximately half the frequency of the HFR peak.

Despite some discrepancies, the qualitative similarity of the model-generated results to the experimentally derived tMTF and phase response curve suggests that the proposed feedback circuit may provide insight into the mechanisms underlying HFRs in cat Y ganglion cells. It can be easily verified that HFRs in the retinal model were produced by axon-mediated feedback onto ganglion cells (See for example Fig. 8). Stimulated ganglion cells excited neighboring axon-bearing amacrine cells via gap junctions. The axon-bearing amacrine cells then strongly inhibited both ganglion cells and other axon-bearing amacrine cells in the surrounding area after a variable delay. A resonance occurs because at input frequencies that are well matched to the dynamics of the axon-mediated feedback loop, the negative phase of the stimulus coincided with the arrival of the axon-mediated inhibition, whereas the positive phase arrived only after the inhibition had declined and the ganglion cells were ready to fire again. In the next two sections, we show how alternative negative feedback loops have difficulty accounting for all of the experimentally observed properties of HFRs, particularly the anomalous phase advance at frequencies approximately half that of the HFR peak.

Axon-mediated feedback loops including graded synaptic output

The axon-mediated feedback loop responsible for HFRs in the retinal model was highly non-linear, primarily involving synaptic interactions between spiking neurons. Could similar results have been obtained using feedback onto non-spiking neurons with graded synaptic output, such as bipolar cells? To investigate this question, we modified the parameters of the retinal model so as to greatly reduce the gain of the axon-mediated feedback onto ganglion cells ($\times 1032$) while greatly increasing the gain of the axon-mediated feedback onto bipolar cells ($\times 32$). Other connection strengths were adjusted, albeit over a much smaller range, so as to make the responses to a stationary 4×4 spot stimulus approximately the same under the two sets of parameters. For a resonance circuit consisting primarily of axon-mediated feedback onto bipolar cells, the multi-unit tMTF exhibited an HFR peak that was qualitatively similar to that produced by the standard model (Fig. 5a) but there was no longer a corresponding abrupt advance in the phase response curve (Fig. 5b). Although negative feedback onto cone and/or bipolar terminals would seem, *a priori*, to provide a likely mechanism for generating HFRs, our results suggest that a strong non-linearity, such as finite firing thresholds, are essential to fully account for the phenomenon.

Linear feedback loops

To further investigate the mechanisms potentially responsible for HFRs in cat Y ganglion cells, including the abrupt advance in the phase response curve, we constructed a simple

linear model from a combination of band-pass filters in series with a harmonic oscillator (Fig. 1c). Parameters were chosen that produced a best fit between the tMTF produced by the combination of linear filters (Fig. 5c, solid line) and that recorded from the retinal model (Fig. 4a). Although both models produced a substantial HFR peak, there was no abrupt shift in the phase response curve obtained from the cascade of linear filters, except for an inflection in the vicinity of the high frequency resonance (Fig. 5d, solid lines). Even when the relative amplitude of the HFR peak in the linear model was increased by a factor of 10 (Fig. 5c, dashed line), there was still no evidence of an abrupt phase advance at approximately half the frequency of the HFR peak (Fig. 5d, dashed line). We were likewise unable to generate an abrupt phase advance in the appropriate frequency range using either a more complex linear model (Troy et al., 1995), which otherwise produced a prominent resonance peak, or by using an additional band pass filter, as opposed to a harmonic oscillator, to model the HFR (not shown). Our results suggest that the prominent kink in the phase response curves recorded from cat Y retinal ganglion cells arises from a non-linear mechanism.

Amplification of low-order harmonics

The prominent kink in the phase response curves recorded from both model and cat Y ganglion cells occurred over regions where low order harmonics of the applied sinusoidal stimulus overlapped with the HFR peak. To investigate this relationship, the standard model was stimulated by 4×4 spots modulated over a broad range of temporal frequencies and the resulting power spectra examined to determine whether harmonics falling within the range of the HFR peak were selectively amplified (Fig. 6a). At stimulus modulation frequencies below approximately 10 Hz, higher harmonics (i.e., 6) were virtually absent from the corresponding power spectra, whereas the lower harmonics exhibited sharply declining amplitudes as their order increased. However, there was a clear amplification of 5th harmonic in response to a 16 Hz modulation ($5 \times 16 = 90$ Hz), of the 3rd harmonic in response to a 24 Hz modulation ($3 \times 24 = 72$ Hz) and especially of the 2nd harmonic in response to a 40 Hz modulation ($2 \times 40 = 80$ Hz). In each of these cases, only those harmonics falling near the HFR peak, approximately between 60 and 90 Hz, were substantially augmented. As the stimulus frequency increased still further, beyond approximately 46 Hz, so that even the 2nd harmonic fell outside the HFR peak, strong amplification was no longer evident.

To more precisely quantify the amplification of low-order harmonics falling near the HFR peak, we plotted response amplitudes for the first few harmonics normalized relative to the response to the fundamental, shown at the top of the panel for comparison (labeled 1:1). The amplitude of the given harmonic, indicated to the upper right of each trace, is plotted as a function of the applied stimulus frequency (solid lines) and as a function of the frequency of the corresponding harmonic, obtained simply by multiplying the fundamental by the appropriate ratio (dotted lines). Low-order harmonics were amplified in response to stimulus frequencies ranging from approximately 20 Hz to 50 Hz. The 2nd harmonic, corresponding to a frequency ratio of 2:1, was most strongly amplified by stimulus frequencies between 30 Hz to 40 Hz, such that corresponding frequencies of the 2nd harmonic followed very closely the HFR peak itself. That such strong amplification of the 2nd harmonic occurred at stimulus frequencies coinciding almost exactly with the region of anomalous phase advance provides compelling evidence that the two phenomena are inextricably related. Higher-order harmonics were less strongly amplified but always at stimulus frequencies such that the corresponding harmonic overlapped the HFR peak.

The earlier mentioned results support the hypothesis that non-linear feedback loops are essential to fully account for the HFRs recorded from cat Y ganglion cells. Linear circuits, such as our cascaded filter model, cannot—by definition—generate harmonics in response

to purely sinusoidal stimuli. Even moderately non-linear circuits, as represented by axon-mediated feedback onto bipolar cells, also appear insufficient to account for the anomalous phase advance seen in both the experimental data and in our standard retinal model. Finally, it seems intuitively reasonable that amplifying the 2nd harmonic, which by definition varies twice as rapidly as the applied stimulus, would cause an anomalous advance in the associated response phase.

Size dependence

Another feature of HFRs captured by the model is their strong dependence on stimulus size. In recordings from cat ganglion cells, HFRs became much more prominent in response to diffuse as opposed to optimal gratings (Frishman et al., 1987). Similar effects were present in the responses of the model ganglion cells as a function of stimulus size (Fig. 7). Temporally modulated spots covering either 1×1 , 2×2 , 4×4 , or 8×8 ganglion cells produced HFRs whose amplitudes increased markedly with stimulus diameter. The high frequency resonance peak produced by the 1×1 spot, which covered only a single ganglion cell, was negligible, showing that neither intrinsic properties nor synaptic mechanisms restricted to the receptive field center made an important contribution to HFRs in the retinal model. A small HFR peak was evident in response to temporal modulations of a 2×2 spot, reflecting partial activation of the axon-mediated feedback circuit. The dip in the responses to slowly varying (~ 3 Hz) modulations of the 2×2 spot was most likely caused by a low frequency resonance in the negative feedback loop created by the serial interactions between the different amacrine cell types. Temporal modulations of the 4×4 , and especially the 8×8 spot, evoked progressively larger HFR peaks, because the stimulus was able to recruit a larger pool of axon-mediated inhibition, thus amplifying the resonance response of the feedback circuit. The location of the HFR peak also depended on stimulus size, first shifting to higher frequencies as the spot diameter was increased and then falling slightly for very large spots. Such size dependence provides further evidence that the underlying mechanisms are non-linear, as the resonance frequency of a harmonic oscillator would be independent of the stimulus intensity or total flux. The shifts in the oscillatory and resonance frequencies predicted by the retinal model are reminiscent of the changes in temporal filtering properties associated with contrast gain control in cat ganglion cells (Shapley & Victor, 1978), which likewise depend on stimulus dimensions and contrast (Shapley & Victor, 1979). The abrupt advance in the phase response curve exhibited a similar dependence on stimulus size, being most prominent for the largest spot.

Dependence on key parameters

HFRs depend on model parameters that determine the effective gain and delay of the axon-mediated negative feedback loop. To quantify how changes in loop gain and delay affect the amplitude and central frequency of the HFR peak, we constructed multi-unit tMTFs in response to a standard 4×4 spot stimulus after systematically varying key model parameters, specifically the inhibition strength (Fig. 8a) and the fixed synaptic delay (Fig. 8b) of the axonal connections. The location and amplitude of the HFR peak were quantified by fitting the tMTF with a combination of a Gaussian and a Lorentzian, as illustrated previously. The results are presented as bar graphs, showing the percent change from the standard values for each of the above two measures, along with the change in tonic firing rate evoked by static presentations of the same stimulus (Figs. 8c, 8d). Increasing the gain of the axon-mediated feedback loop, particularly by increasing the inhibition to both the ganglion cells and the polyaxonal amacrine cells, clearly increased the amplitude of the HFR peak but had a much smaller effect on the frequency. The tonic firing rate diminished steadily with increasing feedback inhibition, which may have confounded some of the effects of feedback gain changes on the shape and location of the HFR peak. On the other hand, increasing the effective delay around the feedback loop produced very clear increases

in the amplitude of the HFR peak, whereas the peak frequency exhibited a clear decrease as a function of axonal latency. Changing the effective delay of the axon-mediated feedback loop had negligible effects on the tonic firing rate, which may account for the relatively clear effects produced on other aspects of the HFR peak. Importantly, changing the gain and delay of the axon-mediated feedback loop, even by proportionately large amounts did not produce gross uncontrolled changes in the resulting tMTFs, indicating that the mechanisms for generating HFRs were robust with respect to key model parameters.

Ocular tremor

Finally, we used the retinal model to investigate how HFRs might contribute to normal visual processing. In particular, we focused on the phenomenon of ocular tremor, an ongoing high frequency jitter in eye position that, in primates, occurs at frequencies between 70–103 Hz (Martinez-Conde et al., 2004). Although the amplitude of these high frequency eye movements is quite small, being on average less than the width of a single photoreceptor, there is experimental and theoretical evidence that ganglion cells can nonetheless respond vigorously to such tiny deflections (Greschner et al., 2002; Hennig et al., 2002). Here, we used the retinal model to investigate whether the responses to high frequency ocular tremor could be amplified by HFRs and if so, what additional visual information such responses might convey.

To investigate the possible importance of HFRs in normal visual processing, we stimulated the retinal model with a naturalistic image (Fig. 9a), either held static or else temporally modulated at frequencies near the HFR peak, the latter being intended to simulate ocular tremor. The resulting retinal output was analyzed in two ways, either as a rate code, based simply on the total number of spikes coming from each image location over the entire recording period (Figs. 9b, 9c), or as a temporal code, based on the peak amplitude in the corresponding power spectra between 60 and 80 Hz (Figs. 9d, 9e). To account for spatial convergence in the early visual processing pathway (Usrey et al., 1999, 2000), the resolution of the reconstructed image was reduced so that each output pixel covered a 2×2 array of ganglion cells, corresponding to a 4×4 pixel neighborhood in the original image. Simply counting spikes yielded a reconstructed image in which spatial contrast was enhanced, a natural consequence of the extensive lateral inhibition incorporated into the model (Fig. 9b). The simulated ocular tremor seemed to have little effect on the rate-based reconstruction, producing only a slight increase in background activity (Fig. 9c). Our key finding was that the image reconstructed from a high frequency temporal code provided a distinct and complementary filtering of the original image from that provided by the rate code, such that large objects were enhanced (Fig. 9d). Moreover, the addition of simulated ocular tremor significantly improved the representation of large objects in the high frequency temporal-code, especially objects that were only poorly reconstructed from static image presentations (Fig. 9e). These results suggest that HFRs, by amplifying the responses to high frequency ocular tremor, may contribute to normal visual processing.

Rate and temporally coded responses, measured across all 2×2 output pixels, were only weakly correlated even under the common influence of the simulated ocular tremor (Fig. 9f), so that it was possible to selectively augment one type of signal without affecting the other. A scatter plot illustrating the covariance of the rate *versus* temporally coded signals did not fall on a straight line, as would be expected if the two measures were entirely dependent, but rather were distributed in two roughly independent clusters, a finding that was confirmed even in the absence of imposed jitter (not shown). Thus, simulated ocular tremor was able to selectively augment the high frequency temporal modulations of output pixels responding to large objects. Indeed, direct inspection of the two reconstructed images shows that they are not simply scaled versions of each other, but rather that the rate and temporal codes represent very different types of spatial filtering.

Ocular tremor is unlikely to be purely sinusoidal, however, but will contain some spectral spread. We therefore asked whether more realistic forms of simulated ocular tremor that included varying amounts of spectral noise would produce similar improvements in temporal coding. To quantify the effects of the simulated ocular tremor, we used the average spectral amplitude between 60 and 80 Hz compared to that elicited by a static image (Fig. 10). Interestingly, a small amount of spectral noise actually increased the effectiveness of the simulated ocular tremor, which then declined as the noise level was raised still further. Presumably, a small amount of spectral spread is helpful for ensuring that the simulated ocular tremor overlaps the HFR peak. In all cases examined, the imposed jitter, regardless of spectral spread, was able to amplify temporally coded information relative to that conveyed by static images. These results indicate the enhancement of temporal coding by ocular tremor is likely to be robust with respect to superimposed random variations in eye position, as long as the jitter frequency and the location of the HFR peak are reasonably well matched.

Discussion

In the cat retina, Y ganglion cells exhibit prominent HFRs in their responses to diffuse, rapidly varying stimuli (Frishman et al., 1987). We used a computational model to investigate whether axon-mediated feedback involving a class of spiking amacrine cells, which are both electrically coupled with—and make strong inhibitory synapses onto—ganglion cells, could account for HFRs in a manner consistent with retinal physiology and anatomy. Multi-unit tMTFs recorded from model ganglion cells exhibited resonance peaks that were qualitatively similar to the HFRs observed experimentally. Moreover, axon-mediated feedback, which was distributed over a wide retinal area, was strongly dependent on stimulus size, producing negligible HFRs in response to small stimuli and prominent HFRs in response to large stimuli, consistent with the size dependence of HFRs observed experimentally. The model also accounted for the anomalous shift in the phase response curves recorded from cat Y ganglion cells at approximately half the central frequency of the HFR peak. Our results suggest that this anomalous phase shift is due to the amplification of low-order harmonics of the applied sinusoidal stimulus. Input frequencies over which the anomalous phase shift is most prominent corresponded very closely to regions where the 2nd harmonic overlapped the HFR peak. Phase response curves generated by axon-mediated feedback directed primarily onto neurons with graded output, such as bipolar cells, as well as the phase response curves generated by linear feedback circuits, never exhibited an anomalous phase advance similar to that present in the experimentally recorded phase plots, even though such models generated HFR peaks that were substantially equivalent to, or in some cases much larger than, those present in cat Y ganglion cells. We concluded that strongly non-linear feedback circuits, such as implemented in our standard model, likely contribute to the responses of cat Y ganglion cells to large, rapidly varying stimuli.

Our results suggest that the generation of HFRs in cat Y ganglion cells can be described by the following hypothetical scenario. In response to a large, rapidly varying input, the activation of Y ganglion cells is postulated to closely track their excitatory input from bipolar cells (Freed & Sterling, 1988). Because the ganglion cells, whose effective time constants are relatively short—on the order of only a few ms (O'Brien et al., 2002), respond to the rising phase of their excitatory input, they in turn activate neighboring axon-bearing amacrine cells via gap junctions (Vaney, 1991, 1994). These axon-bearing amacrine cells in turn provide a powerful source of delayed inhibition, distributed over a wide area, whose peak coincides with the falling phase of the excitatory input. By the time the next stimulus cycle begins, the axon-mediated inhibition, also governed by a relatively rapid kinetics, will have largely terminated, thus freeing the ganglion cells to respond at the next rising phase of the excitatory input. Local inhibition from small diameter, non-spiking amacrine cells,

whose effective time constants are on the order of tens of ms, would be minimally recruited by high frequency stimulation. Moreover, the suppression of narrow field amacrine cells via axon-mediated inhibition (O'Brien et al., 2003) further amplifies ganglion cell responses to high frequency stimulation via disinhibition. Finally, local gap junctions and long-range synaptic interactions between the axon-bearing amacrine cells help to sharpen the time course of their widely distributed inhibition, thus sharpening the corresponding HFR peak.

The amplitude and location of the HFR peak recorded from the model ganglion cells depended in a systematic way on key parameters that determined the overall gain and delay of the axon mediated feedback loop. In principle, it may be possible to experimentally manipulate the physiological equivalents of these key model parameters, thus testing critical aspects of the proposed model. For instance, the gain of the axon-mediated feedback loop could be reduced either by blocking long-range inhibition, the generation of action potentials, or by blocking gap junctions between ganglion cells and axon-bearing amacrine cells. Likewise, by cooling the inner retina it may be possible to increase axonal delays.

Given the strong similarities between alpha ganglion cells in the cat retina and parasol ganglion cells in the primate retina (Peichl, 1991), especially the similarities in their patterns of tracer coupling to axon-bearing amacrine cells (Dacey & Brace, 1992; Vaney, 1994; Jacoby et al., 1996), axon-mediated feedback may be present in the primate retina as well. The tMTFs recorded from peripheral M cells in response to large time varying stimuli exhibit HFRs similar to those seen in the cat retina (Solomon et al., 2002). In addition, small HFRs are evident in the responses of P ganglion cells to luminance gratings (Martin et al., 2001) and a ringing at approximately 75 Hz is seen in the impulse response of M ganglion cells to large, high contrast stimuli (Lee et al., 1994). More significantly, spectral peaks in the appropriate frequency range are clearly present in primate (Frishman et al., 2000) and human (De Carli et al., 2001) ERGs. The conclusions of the present study may therefore be relevant to the investigation of HFRs in the primate retina as well. The resonance peaks recorded from cat X ganglion cells in response to diffuse stimuli are of a different character than those recorded from Y cells, being less distinct, and the phase response curves recorded from X ganglion cells do not exhibit an anomalous positive shift at approximately half the central frequency of the HFR peak. Thus, despite the fact that both X and Y ganglion cells exhibit robust HFRs, the underlying mechanisms may be quite different. HFRs have also been observed in other ganglion cell types (Troy et al., 1995), although further characterization will be necessary to determine whether distinct mechanisms are involved.

High-frequency-oscillatory-potentials (HFOPs), evoked by stationary or slowly varying stimuli, have been recorded in cat (Neuenschwander & Singer, 1996; Neuenschwander et al., 1999) and other vertebrate retinas, including frog (Ishikane et al., 1999, 2005), mudpuppy (Wachtmeister & Dowling, 1978), rabbit (Ariel et al., 1983) and primates (Wachtmeister, 1998), using single and multi-unit recordings, as well as local field potentials and ERGs. HFRs, on the other hand, are typically inferred from single unit responses to rapidly varying stimuli. Because HFRs and HFOPs involve high frequency modulations in response to large stimuli, the most parsimonious hypothesis is that they derive from a common set of cellular and/or synaptic mechanisms. The present model, which was originally developed to account for the sizedependent, stimulus-specific oscillatory responses of cat Y ganglion cells (Kenyon et al., 2003), demonstrates that, in principle, axon-mediated feedback can explain the main experimental properties of HFRs and HFOPs. By recording HFRs and HFOPs in the same preparation, future experiments should be able to determine whether both phenomena share a common underlying mechanism. Specifically, only a common underlying mechanism, or set of mechanisms, could readily explain a strong covariation in the amplitudes and peak frequencies of HFRs and HFOPs as a function of stimulus parameters, such as size, wavelength and contrast.

Finally, we considered how HFRs might contribute to normal visual processing via the mechanism of ocular jitter, even though the frequencies involved are beyond the threshold for conscious visual perception (Spekreijse et al., 1971; Swanson et al., 1987). Our results suggest that HFR circuitry could amplify the responses to ocular tremor, conveying information that is distinct from, and complementary to, that conveyed by the mean firing rate. The idea that in addition to a conventional rate code, the retina also uses a complementary temporal code has been previously suggested (Meister & Berry, 1999). Although the absolute shifts in eye position produced by ocular tremor are very small, similar deflections have been shown to increase the firing rate and the information content of ganglion cell spike trains in the turtle retina (Greschner et al., 2002). Using computer models, it has further been argued that ocular tremor could increase spatial acuity by exploiting non-linear subunits (Hennig et al., 2002). Our simulation of ocular tremor was, by necessity, very crude, as our model ganglion cells were nearly an order of magnitude less sensitive to temporal modulations than are ganglion cells in the cat retina. Nonetheless, the model was sufficient to demonstrate how, in principle, HFRs could amplify responses to high frequency ocular tremor, thereby selectively enhancing the representation of large stimuli.

References

- Ariel M, Daw NW, Rader RK. Rhythmicity in rabbit retinal ganglion cell responses. *Vision Research*. 1983; 23:1485–1493. [PubMed: 6666049]
- Dacey DM, Brace S. A coupled network for parasol but not midget ganglion cells in the primate retina. *Visual Neuroscience*. 1992; 9:279–290. [PubMed: 1390387]
- De Carli F, Narici L, Canovaro P, Carozzo S, Agazzi E, Sannita WG. Stimulus- and frequency-specific oscillatory mass responses to visual stimulation in man. *Clinical Electroencephalography*. 2001; 32:145–151. [PubMed: 11512378]
- Euler T, Masland RH. Light-evoked responses of bipolar cells in a mammalian retina. *Journal of Neurophysiology*. 2000; 83:1817–1829. [PubMed: 10758094]
- Euler T, Wassle H. Different contributions of GABAA and GABAC receptors to rod and cone bipolar cells in a rat retinal slice preparation. *Journal of Neurophysiology*. 1998; 79:1384–1395. [PubMed: 9497419]
- Fahey PK, Burkhardt DA. Effects of light adaptation on contrast processing in bipolar cells in the retina. *Visual Neuroscience*. 2001; 18:581–597. [PubMed: 11829304]
- Foerster MH, van de Grind WA, Grusser OJ. The response of cat horizontal cells to flicker stimuli of different area, intensity and frequency. *Experimental Brain Research*. 1977; 29:367–385.
- Freed MA. Rate of quantal excitation to a retinal ganglion cell evoked by sensory input. *Journal of Neurophysiology*. 2000; 83:2956–2966.
- Freed MA, Pflug R, Kolb H, Nelson R. ON-OFF amacrine cells in cat retina. *Journal of Comparative Neurology*. 1996; 364:556–566. [PubMed: 8820883]
- Freed MA, Smith RG, Sterling P. Timing of quantal release from the retinal bipolar terminal is regulated by a feedback circuit. *Neuron*. 2003; 38:89–101. [PubMed: 12691667]
- Freed MA, Sterling P. The ON-alpha ganglion cell of the cat retina and its presynaptic cell types. *Journal of Neuroscience*. 1988; 8:2303–2320. [PubMed: 3249227]
- Frishman LJ, Freeman AW, Troy JB, Schweitzer-Tong DE, Enroth-Cugell C. Spatiotemporal frequency responses of cat retinal ganglion cells. *Journal of General Physiology*. 1987; 89:599–628. [PubMed: 3585279]
- Frishman LJ, Saszik S, Harwerth RS, Viswanathan S, Li Y, Smith EL 3rd, Robson JG, Barnes G. Effects of experimental glaucoma in macaques on the multifocal ERG. Multifocal ERG in laser-induced glaucoma. *Documenta Ophthalmologica*. 2000; 100:231–251. [PubMed: 11142748]
- Frishman LJ, Sieving PA. Evidence for two sites of adaptation affecting the dark-adapted ERG of cats and primates. *Vision Research*. 1995; 35:435–442. [PubMed: 7892737]

- Greschner M, Bongard M, Rujan P, Ammermuller J. Retinal ganglion cell synchronization by fixational eye movements improves feature estimation. *Nature Neuroscience*. 2002; 5:341–347.
- Hennig MH, Kerscher NJ, Funke K, Worgotter F. Stochastic resonance in visual cortical neurons: Does the eye-tremor actually improve visual acuity? *Neurocomputing 10th Computational Neuroscience Meeting (CSN 01) Computational Neuroscience: Trends in Research 2002*, July 2001, Monterey, CA, USA. 2002; 44/46:115–120.
- Hurley JB. Shedding light on adaptation. *Journal of General Physiology*. 2002; 119:125–128. [PubMed: 11815663]
- Ishikane H, Gangi M, Honda S, Tachibana M. Synchronized retinal oscillations encode essential information for escape behavior in frogs. *Nature Neuroscience*. 2005; 8:1087–1095. Epub 2005 Jul. 3.
- Ishikane H, Kawana A, Tachibana M. Short- and long-range synchronous activities in dimming detectors of the frog retina. *Visual Neuroscience*. 1999; 16:1001–1014. [PubMed: 10614583]
- Jacoby R, Stafford D, Kouyama N, Marshak D. Synaptic inputs to ON parasol ganglion cells in the primate retina. *Journal of Neuroscience*. 1996; 16:8041–8056. [PubMed: 8987830]
- Kenyon, GT.; Harvey, NR.; Stephens, GJ.; Theiler, J. *Proceedings SPIE: Applications of Digital Image Processing XXVII*. Denver: 2004a. Dynamic segmentation of gray-scale images in a computer model of the mammalian retina.
- Kenyon GT, Marshak DW. Gap junctions with amacrine cells provide a feedback pathway for ganglion cells within the retina. *Proceedings of the Royal Society London Series B Biological Sciences*. 1998; 265:919–925.
- Kenyon GT, Moore B, Jeffs J, Denning KS, Stephens GJ, Travis BJ, George JS, Theiler J, Marshak DW. A model of high-frequency oscillatory potentials in retinal ganglion cells. *Visual Neuroscience*. 2003; 20:465–480. [PubMed: 14977326]
- Kenyon GT, Theiler J, George JS, Travis BJ, Marshak DW. Correlated firing improves stimulus discrimination in a retinal model. *Neural Computation*. 2004b; 16:2261–2291. [PubMed: 15476601]
- Kenyon GT, Travis BJ, Theiler J, George JS, Stephens GJ, Marshak DW. Stimulus-specific oscillations in a retinal model. *IEEE Transactions on Neural Networks*. 2004c; 15:1083–1091. [PubMed: 15484885]
- Kolb H, Nelson R. OFF-alpha and OFF-beta ganglion cells in cat retina: II. Neural circuitry as revealed by electron microscopy of HRP stains. *Journal of Comparative Neurology*. 1993; 329:85–110. [PubMed: 8454727]
- Lee BB, Pokorny J, Smith VC, Kremers J. Responses to pulses and sinusoids in macaque ganglion cells. *Vision Research*. 1994; 34:3081–3096. [PubMed: 7975341]
- Martin PR, Lee BB, White AJ, Solomon SG, Rüttger L. Chromatic sensitivity of ganglion cells in the peripheral primate retina. *Nature*. 2001; 410:933–936. [PubMed: 11309618]
- Martinez-Conde S, Macknik SL, Hubel DH. The role of fixational eye movements in visual perception. *Nature Reviews Neuroscience*. 2004; 5:229–2240.
- Meister M, Berry MJ 2nd. The neural code of the retina. *Neuron*. 1999; 22:435–450. [PubMed: 10197525]
- Neuenschwander S, Castelo-Branco M, Singer W. Synchronous oscillations in the cat retina. *Vision Research*. 1999; 39:2485–2497. [PubMed: 10396618]
- Neuenschwander S, Singer W. Long-range synchronization of oscillatory light responses in the cat retina and lateral geniculate nucleus. *Nature*. 1996; 379:728–732. [PubMed: 8602219]
- O'Brien BJ, Isayama T, Richardson R, Berson DM. Intrinsic physiological properties of cat retinal ganglion cells. *Journal of Physiology*. 2002; 538:787–802. [PubMed: 11826165]
- O'Brien BJ, Richardson RC, Berson DM. Inhibitory network properties shaping the light evoked responses of cat alpha retinal ganglion cells. *Visual Neuroscience*. 2003; 20:351–361. [PubMed: 14658764]
- Passaglia CL, Enroth-Cugell C, Troy JB. Effects of remote stimulation on the mean firing rate of cat retinal ganglion cells. *Journal of Neuroscience*. 2001; 21:5794–5803. [PubMed: 11466451]

- Peichl L. Alpha ganglion cells in mammalian retinae: Common properties, species differences, and some comments on other ganglion cells. *Visual Neuroscience*. 1991; 7:155–169. [PubMed: 1931799]
- Press, WH.; Flannery, BP.; Teukolsky, SA.; Vetterling, WT. *Numerical Recipes*. Cambridge University Press; Cambridge: 1986.
- Reich DS, Victor JD, Knight BW, Ozaki T, Kaplan E. Response variability and timing precision of neuronal spike trains in vivo. *Journal of Neurophysiology*. 1997; 77:2836–2841. [PubMed: 9163398]
- Robinson DW, Chalupa LM. The intrinsic temporal properties of alpha and beta retinal ganglion cells are equivalent. *Current Biology*. 1997; 7:366–374. [PubMed: 9197237]
- Schnapf JL, Nunn BJ, Meister M, Baylor DA. Visual transduction in cones of the monkey *Macaca fascicularis*. *Journal of Physiology*. 1990; 427:681–713. [PubMed: 2100987]
- Shapley R. Retinal physiology: Adapting to the changing scene. *Current Biology*. 1997; 7:R421–423. [PubMed: 9210365]
- Shapley RM, Victor JD. The effect of contrast on the transfer properties of cat retinal ganglion cells. *Journal of Physiology*. 1978; 285:275–298. [PubMed: 745079]
- Shapley RM, Victor JD. Nonlinear spatial summation and the contrast gain control of cat retinal ganglion cells. *Journal of Physiology*. 1979; 290:141–161. [PubMed: 469742]
- Shapley RM, Victor JD. How the contrast gain control modifies the frequency responses of cat retinal ganglion cells. *Journal of Physiology*. 1981; 318:161–179. [PubMed: 7320887]
- Shields CR, Lukasiewicz PD. Spike-Dependent GABA Inputs to Bipolar Cell Axon Terminals Contribute to Lateral Inhibition of Retinal Ganglion Cells. *Journal of Neurophysiology*. 2003; 89:2449–2458. [PubMed: 12611993]
- Smith RG. Simulation of an anatomically defined local circuit: The cone-horizontal cell network in cat retina. *Visual Neuroscience*. 1995; 12:545–561. [PubMed: 7654610]
- Solessio E, Vigh J, Cuenca N, Rapp K, Lasater EM. Membrane properties of an unusual intrinsically oscillating, wide-field teleost retinal amacrine cell. *Journal of Physiology*. 2002; 544:831–847. [PubMed: 12411527]
- Solomon SG, Martin PR, White AJ, Rüttiger L, Lee BB. Modulation sensitivity of ganglion cells in peripheral retina of macaque. *Vision Research*. 2002; 42:2893–2898. [PubMed: 12450500]
- Spekreijse H, van Norren D, van den Berg TJ. Flicker responses in monkey lateral geniculate nucleus and human perception of flicker. *Proceedings of the National Academy of Science USA*. 1971; 68:2802–2805.
- Swanson WH, Ueno T, Smith VC, Pokorny J. Temporal modulation sensitivity and pulse-detection thresholds for chromatic and luminance perturbations. *Journal of the Optical Society of America A*. 1987; 4:1992–2005.
- Troy JB, Schweitzer-Tong DE, Enroth-Cugell C. Receptive-field properties of Q retinal ganglion cells of the cat. *Visual Neuroscience*. 1995; 12:285–300. [PubMed: 7786850]
- Usrey WM, Alonso JM, Reid RC. Synaptic interactions between thalamic inputs to simple cells in cat visual cortex. *Journal of Neuroscience*. 2000; 20:5461–5467. [PubMed: 10884329]
- Usrey WM, Reppas JB, Reid RC. Specificity and strength of retinogeniculate connections. *Journal of Neurophysiology*. 1999; 82:3527–3540. [PubMed: 10601479]
- Vaney DI. Many diverse types of retinal neurons show tracer coupling when injected with biocytin or Neurobiotin. *Neuroscience Letters*. 1991; 125:187–190. [PubMed: 1715532]
- Vaney DI. Patterns of neuronal coupling in the retina. *Progress in Retinal and Eye Research*. 1994; 13:301–355.
- Victor JD, Shapley RM. Receptive field mechanisms of cat X and Y retinal ganglion cells. *Journal of General Physiology*. 1979; 74:275–98. [PubMed: 490143]
- Vigh J, Solessio E, Morgans CW, Lasater EM. Ionic Mechanisms Mediating Oscillatory Membrane Potentials in Wide-field Retinal Amacrine Cells. *Journal of Neurophysiology*. 2003; 90:431–443. [PubMed: 12649310]
- Wachtmeister L. Oscillatory potentials in the retina: What do they reveal. *Progress in Retinal and Eye Research*. 1998; 17:485–521. [PubMed: 9777648]

Wachtmeister L, Dowling JE. The oscillatory potentials of the mudpuppy retina. Investigations in Ophthalmological and Visual Science. 1978; 17:1176–1188.

Fig. 1.

Models of HFRs. **(A, B)** Axon-mediated feedback model. The model contained five cells types: bipolar (BP) cells, small (SA), large (LA) and poly-axonal (PA) amacrine cells, and alpha ganglion (GC) cells. **(A)** Feed forward and feedback interactions. Excitation from BPs was balanced by a combination of feed forward and feedback inhibition from the SAs and LAs, both local, non-spiking amacrine cell types. PAs were excited locally via electrical synapses with GCs. PA axons mediated widely distributed inhibition directed primarily to the GCs and other PAs, forming a negative feedback loop responsible for HFRs. **(B)** Serial inhibition. The three different amacrine cell types regulated each other through a local negative feedback loop. (Not shown: the LAs were electrically coupled to each other and the PAs received a small excitatory input from the BPs and made weaker long-range inhibitory synapses onto the other cell types. **(C)** Linear model. A cascade of three linear filters, consisting of feed forward and feedback inhibition in series with a harmonic oscillator. The FF and FB modules implemented a broadly tuned band-pass filter with peak output around 15 Hz. The HO was narrowly tuned to produce a sharp HFR at around 72 Hz.

Fig. 2.

Model generated mPSTHs in response to sinusoidally varying stimuli. Solid lines: Trial-averaged responses of all 16 model GCs activated by a uniform 4×4 spot, binned relative to the phase of the applied stimulus. Temporal modulation frequencies noted at the upper right of each plot. Modulation amplitudes were clearly elevated at 15 Hz and 73 Hz. Stimulus contrast (peak-trough/average intensity) was 50%. Raster plots: (Dark gray ticks) Ganglion cells (Light gray ticks), Axon-bearing amacrine cells. Periodic clustering was most evident at 15 Hz.

Fig. 3.

Model generated responses relative to stimulus phase. (Left column) Fundamental Fourier components (solid black lines), extracted from the corresponding mPSTHs, shown superimposed on representative raster plots (dark and light gray ticks, ganglion cells and axon-bearing amacrine cells, respectively). Time scale was adjusted so that all plots included the same number of stimulus cycles. The number of rows in each raster was inversely proportional to the duration, so as to approximately normalize the total number of time steps. Periodic clustering was evident at both 15 Hz and at 73 Hz. (Right column) All 100 fundamental Fourier components plotted relative to the stimulus phase using a fixed vertical offset between traces. Two bands of elevated response, centered around 15 Hz and 73 Hz, are evident, as well as an inflection in the response phase between 30 Hz and 40 Hz.

Fig. 4.

HFRs of model and cat Y ganglion cells. **(a)** Multi-unit tMTF recorded from all 16 model ganglion cells responding to a 4×4 sinusoidally varying stimulus. Circles: simulation data (for clarity, only one-quarter of the data points were shown). Line: Best fit of the multi-unit tMTF by a sum of Gaussian and Lorentzian functions. **(b)** tMTF recorded from a cat Y ganglion cells in response to a diffuse grating. Circles: experimental data. Line: Best fit. In both the model and experimental data, the maximum response occurred over a broad low frequency band between 10–20 Hz but there was also a prominent HFR around 70 Hz. **(c)** Model generated multi-unit phase response curve. **(d)** Phase response curve from cat Y ganglion cells. In both the model and experimental data, the response phase exhibited an anomalous positive shift at approximately one-half the central frequency of the HFR peak. Experimental data re-plotted from Frishman et al. (1987)

Fig. 5.

Graded and linear models of HFRs. (Left column) graded model. Axon-mediated inhibition was redirected from spiking ganglion cells to non-spiking bipolar cells that produced graded synaptic output. **(a)** Multi-unit tMTF, **(b)** Multi-unit phase response curve. Although the graded feedback model produced a prominent HFR there was no corresponding shift in the phase response curve. (Right column) linear model. A cascade of band pass filters, representing feedforward and feedback inhibition, were combined in series with a harmonic oscillator. **(c)** Best-fit theoretical tMTF. Dashed line: modified linear model in which the amplitude of the HFR peak was increased by a factor of 10. **(d)** Solid line: phase response curve from best-fit linear model. Dashed line: phase plot from modified linear model. There was no anomalous shift in the phase response curves obtained from either linear model.

Fig. 6.

Amplification of low-order harmonics. **(a)** Normalized power spectra computed from mPSTHs obtained in response to a 4×4 spot modulated at various frequencies, indicated to the lower left of each trace. Harmonics falling near the HFR peak, approximately 60 Hz to 90 Hz, were selectively amplified. **(b)** Top trace: normalized response to time varying 4×4 spot stimulus at the fundamental frequency (1:1). Bottom Traces: normalized amplitudes of the 2nd, 3rd, 4th, and 5th harmonics, indicated to the upper right of each trace, relative to the amplitude of the fundamental. Harmonic amplitudes plotted as a function of the stimulus frequency (Solid lines) and a function of the corresponding harmonic frequency (dotted line). Harmonic frequencies that overlapped the HFR peak were selectively amplified, especially the 2nd harmonic, suggesting a possible interpretation of the anomalous shift in the phase response curve at stimulus frequencies between 30 Hz to 40 Hz.

Fig. 7. HFRs increase with stimulus size. **(a)** Multi-unit tMTFs computed in response to sinusoidally modulated spots covering 1×1 , 2×2 , 4×4 , and 8×8 model ganglion cells. Resonance peaks became larger with increasing spot size. **(b)** Multi-unit phase plots in response to the same set of spot stimuli. The anomalous shift in the phase response curves became more prominent as the spot size was increased.

Fig. 8.

Dependence of HFRs on key model parameters. Left column: axon-mediated feedback inhibition was reduced by 5% or 25%, or increased to 200%, of the standard value. Right column: The fixed synaptic delay in the axon-mediated feedback pathway was reduced and increased by 1 ms. **(a, b)** Multi-unit tMTFs obtained in response to a 4×4 spot stimulus. **(c, d)** Bar graphs showing % change from the standard value: 1st row: HFR peak amplitude. 2nd row: HFR peak frequency. 3rd row: tonic firing rate. HFR peak amplitudes increased as a function of both the gain and delay of the axon-mediated feedback loop. Overall the model was robust with respect to changes in key parameter values.

Fig. 9.

Effects of simulated ocular tremor on rate and temporally coded information. **(a)** Original image (256×256). **(b, c)** Image reconstruction based on a simple rate-code. The intensity of each pixel was set proportional to the total number of spikes arising from a 2×2 array of neighboring ganglion cells. **(b)** Without simulated ocular tremor. **(c)** After adding a 72 Hz temporal modulation to the input image. Simulated ocular tremor produced only a small increase in background activity. **(d, e)** Reconstruction based on a temporal-code. Each pixel in the output image was set proportional to the peak power between 60 to 80 Hz. Large foreground objects were selectively enhanced. **(d)** Without simulated ocular tremor, **(e)** with added jitter. Simulated ocular tremor improved the reconstruction of large image features. For all images, average luminance and contrast were scaled to 0 and 1, respectively. Bins more than one standard deviation below the mean were set to black, whereas bins more than four standard deviations above the mean were set to white. **(f)** Covariance of rate-and temporally-coded signals. Each point plots the peak power between 60–80 Hz *versus* the number of spikes for each 2×2 ganglion cell neighborhood. Despite strong correlations between the rate-and temporally-coded signals, points were scattered broadly around the best fit regression line, showing that the two information channels were partially independent.

Fig. 10.

Effects of spectral spread in simulated ocular tremor. Additional Fourier components were added to the simulated ocular tremor in random phase and with weighted amplitudes drawn from a Gaussian distribution of width σ . **(a)** Representative added jitter with either 1 Hz spectral spread (black trace) or 16 Hz spectral spread (gray trace). **(b)** Bar graph showing the average temporally-coded output, measured as the average power between 60 to 80 Hz, as a function of the degree of spectral spread added to the simulated ocular tremor, normalized relative to the responses to a static image. Small amounts of spectral noise actually boosted the average amplitude of temporally-coded signals relative to a pure sinusoidal modulation. Over the range tested, temporally-coded signals were always boosted by the imposed jitter, relative to the static image, regardless of the amount of spectral spread.