LINKING THE COMPUTATIONAL STRUCTURE
OF VARIANCE ADAPTATION
TO BIOPHYSICAL MECHANISMS

A DISSERTATION
SUBMITTED TO THE DEPARTMENT OF ELECTRICAL ENGINEERING
OF STANFORD UNIVERSITY
IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

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August 2011
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ABSTRACT

Neurons have a limited dynamic range. To more efficiently encode the large range of natural inputs, neural circuits adapt by dynamically changing their output range as a function of the input statistics. Variance adaptation provides an informative example of this process, whereby neurons change their response characteristics as a function of variance of their input.

When their input distribution changes, sensory systems shift and scale their response curves to efficiently cover the new range of input values and they focus on different segments of the frequency spectrum, for example by choosing to average out the noise in a low signal-to-noise ratio environment by low-pass filtering their input and sacrificing resolution. In multiple sensory systems, adaptation to the variance of a sensory input changes the sensitivity, kinetics and average response over timescales ranging from < 100 ms to tens of seconds. Here we present a simple biophysically relevant model of retinal contrast adaptation that accurately captures both the membrane potential response and all adaptive properties. The adaptive component of this model is a first-order kinetic process of the type used to describe ion channel gating and synaptic transmission. We conclude that all adaptive dynamics can be accounted for by depletion of a signaling mechanism, and that contrast adaptation can be explained as adaptation to the mean of a thresholded signal. A diverse set of adaptive properties that implement theoretical principles of efficient coding can be generated by a single type of molecule or synapse with just a few microscopic states.

The LNK model helps to highlight important aspects of adaptation by letting us focus on individual computational blocks separately. By using the LNK model, we
investigate the source of the adaptive process in On-Off retinal ganglion cells, which show strong changes in their kinetics as a function of contrast. By analyzing properties of the LNK model, we conclude that most of the adaptive effect is due to differences in the threshold of the two pathways, with a smaller contribution from different adaptive kinetics. Adaptive temporal decorrelation in the retina arises due to differential thresholding in two parallel neural pathways.
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CHAPTER I - INTRODUCTION

The range of natural inputs exceeds the range of possible outputs for neurons. As a result, neural circuits adapt so as to more efficiently encode the recent history of inputs. Although the exact nature of this adaptation varies within the nervous system, the basic principles are the same. As a response to a changing input feature, the neuron shifts or scales its input-output curve, matching the new input distribution with its limited range of outputs.

The retina distinguishes itself as a subsystem that can adapt to many different features of the natural stimuli. These stimulus features range from simple statistics like a shift in mean or the variance of the input distribution to much more complex properties of the stimuli such as a change in the dominant spatial frequency or a shift from local to global motion (Shapley and Victor, 1978; Hosoya et al., 2005; Baccus et al., 2008). Although all of these changes in the dynamical properties are classified as adaptation, the way they are implemented vary greatly. Some forms of adaptation use local biophysical sites in individual neurons, and whereas others appear to be the result of multiple neuronal pathways interacting with each other. How and where in the retina most of these forms of adaptation occur are yet to be studied in detail. The main purpose of this work is to take adaptation to a specific feature in the retina as an example and build a simple computational framework that replicates retinal responses accurately, and does this using biophysically related building blocks that can later be analyzed in detail to shed light into the possible biophysical elements leading to adaptation. A further goal is to inspect the possibility of using the same framework and methodology on
understanding more complex forms of adaptation in the retina or similar processes in other parts of the nervous system.

The example that will be used is a widespread adaptation process that occurs in response to a change in the magnitude of fluctuations around a mean value, or the variance of a sensory input (Laughlin, 1989). Variance adaptation is known to occur not only in the retina but in many sensory systems, including the vertebrate retina and visual cortex, fly visual system, and the avian auditory forebrain (Fairhall et al., 2001; Nagel and Doupe, 2006; Ohzawa et al., 1985; Shapley and Victor, 1978; Smirnakis et al., 1997).

When the stimulus environment changes from a low to high variance a similar list of changes occur with a very fast time constant on the order of 100 ms in all of these systems: The sensitivity of the neurons decreases which is a result of the above-mentioned scaling of the input-output curve. Doing this, the neurons avoid saturation and the loss of information at high intensity values that were not present previously in its input distribution. Also temporal filtering accelerates, resulting in a higher bandwidth in responses. Finally the average response increases, which is observed as a depolarization in membrane potential baseline. (Baccus and Meister, 2002; Chander and Chichilnisky, 2001; Kim and Rieke, 2001; Nagel and Doupe, 2006). As the environment maintains a high variance, slow changes occur on the order of 1-10 s that are comprised mostly of a slow decay in the average response that opposes the previous fast change in baseline. (Baccus and Meister, 2002; Fairhall et al., 2001; Nagel and Doupe, 2006). Upon a switch from high to low contrast all these changes reverse direction. The sensitivity increases, the temporal filtering becomes slower and the average response decreases. The time constants for the slow component of adaptation are asymmetric; with the baseline
decaying faster in high contrast than it rises in low contrast. It is possible to explain the shifts in the baseline membrane potential by looking at the slow baseline change as a homeostatic readjustment to the fast baseline change that occurs at the contrast switch. The baseline adjusts back to a steady state level as the neuron gets more samples from the new input distribution and computes a more accurate value for the new variance. Since switching from a high to low variance distribution involves many values that were already present in the previous distribution, this readjustment takes longer, resulting in the asymmetry of slow component of adaptation. The remarkable similarity of these properties across species and sensory systems indicates a strong commonality in the process of encoding signals that vary in amplitude (Baccus, 2006; Baccus and Meister, 2002; Fairhall et al., 2001; Nagel and Doupe, 2006).

In the vertebrate retina, contrast adaptation can be observed widely among ganglion cells and some amacrine and bipolar cells, but there is diversity in the adaptive strategies of different cell populations, with the strength of contrast adaptive changes varying between different cell types. For example, Off-type cells change their gain more than On-type cells, and On cells show less of a change in temporal processing (Beaudoin et al., 2008; Chander and Chichilnisky, 2001). Among all the amacrine cell types, transient amacrine cells adapt more strongly than sustained amacrine cells. Bipolar cells also vary in their adaptive properties, with some cells not adapting, whereas others changing only their gain or their temporal processing, or not exhibiting slow changes in baseline (Baccus and Meister, 2002; Rieke, 2001).

There is also diversity in the potential mechanisms that have been proposed for contrast adaptation in retinal cells (Demb, 2008). Photoreceptors and horizontal cells do
not change their properties upon a contrast switch, which indicates that there is no site of contrast adaptation in the phototransduction cascade. As some bipolar cells adapt, it is natural to think of an adapting mechanisms being present either just before or after the synapse from the photoreceptors to some bipolar cells. It has been suggested that a postsynaptic mechanisms in the bipolar cell dendritic tree may play a role in bipolar cell contrast adaptation. A large amount of adaptation occurs as the signal travels through the synapse from the bipolar cells to ganglion cells (Beaudoin et al., 2007; Zaghloul et al., 2005). A change in basal vesicle release is proposed to cause the slow component of contrast adaptation, and another calcium related mechanism, such as channel inactivation, might cause fast adaptation although both of these claims has yet to be analyzed in detail (Beaudoin et al., 2008; Demb, 2008; Manookin and Demb, 2006). There is additional adaptation that occurs after the signal reaches the ganglion cell soma during spike generation, and inactivation of voltage-dependent Na channels has been shown to quickly change the gain of the cell (Kim and Rieke, 2003). Although it has been shown that inhibition is not necessary for contrast adaptation to occur, amacrine cells in the retina has many different types and some of these cell types have been related with more complex types of adaptation that may be linked with contrast adapting mechanisms. So the role of the amacrine cells in modulating adaptation has not yet been understood in detail.

Because of the apparent complexity and diversity of related changes and also because contrast adaptation manifests itself in different ways in various cell types both in the retina and across sensory systems in general, building a quantitative model that captures all adaptive changes and can be used as a framework to better understand
variance adaptation has been a challenge. Several models have been proposed for visual contrast adaptation (Gaudry and Reinagel, 2007; Mante et al., 2008; Shapley and Victor, 1979), yet these focus on only few aspects of adaptation or use abstract components that do not have a clear connection to potential biophysical mechanisms. In addition, previous efforts to describe the rules of contrast adaptation using a model were only constrained by the firing rate of spiking neurons, and not the membrane potential response. Although how spiking contributes to adaptation has been explained and analyzed in detail, since a considerable amount of adaptation occurs before spike generation, this helps us understand only partially how retinal cells adapt to contrast.

**Building a model that adapts to contrast**

In the second chapter of this thesis, I explain the structure of a model that links mechanism level operations to computational interpretation using simple building blocks that have previously been used in replicating the behavior of biophysical mechanisms. I use this model to accurately predict the intracellular membrane potential of retinal neurons across a wide range of contrasts. Then I use this simple model that captures all adaptive properties while having a natural relationship to biophysical properties to gain insight into how its mechanics give rise to the multiple properties of adaptation.

**Using the model to make simple interpretations of apparently complex adaptation**

In the third chapter, I use the simplicity of model building blocks to extend our analysis into more complex cell types and more complex types of adaptation. The first example of this chapter is about understanding how contrast adaptation can become stronger by the interaction of multiple pathways in On-Off cells. Strong signals are present in many sensory environments, including high luminance, high contrast, fast
velocity or loud auditory stimuli, and one of the prominent changes that happens when
the input to a neuron becomes stronger is to decrease the sensitivity. A second aspect of
adaptation to changes in stimulus strength involves a change in the preferred stimulus
feature, which manifests itself as a change in spatiotemporal filtering. Natural signals
contain a larger fraction of low temporal frequencies, and thus when the signal-to-noise
ratio of is low, it becomes more efficient to low-pass the input signal, even if it means
losing temporal resolution. The retina makes use of this approach both in low light
intensity and low variance environments. As the SNR of the input decreases the dynamics
for the relevant adapting block changes to discard more of the higher frequencies. At high
SNR, the changes reverse direction, because cells can take advantage of the less noisy
environment to reduce correlations in the input, and thus the temporal response becomes
faster and more differentiating (Atick, 1992; Baccus, 2006; Baccus and Meister, 2002;
Nagel and Doupe, 2006; Singh and Theunissen, 2003; Van Hateren, 1993). This is also
true when the spatial aspects of the inputs are considered, meaning during low luminance,
receptive field centers are larger and surrounds are weaker. (Atick, 1992; Barlow et al.,
1957; De Valois et al., 1974; Enroth-Cugell and Robson, 1966; Van Hateren, 1993)

Here I analyze On-Off amacrine and ganglion cells, which I find to have strong
adaptive changes in temporal differentiation with contrast. The biophysical circuitry that
causes this differentiation is not well understood because the resulting dynamics are
highly nonlinear and also multiple pathways possibly combine to modulate different
aspects of this adaptive change. Using pharmacology and a two-pathway adaptive model,
I first show that it is possible to separate responses coming from different pathways in the
retinal circuitry. This allows us to look at the adaptive properties of these two pathways
in isolation which would be very difficult experimentally. Then further analysis of individual building blocks assess the separate contribution of thresholds and adaptation in each of the two pathways to determine which components produce changes in temporal differentiation. I find that simple building blocks in multiple adapting pathways can combine to produce more complex and stronger adaptation.

The second example for this chapter is on how the same framework can be used in building models for more complex adaptation. I use a newly discovered phenomenon in the retina as an example on how multiple adaptive pathways can be combined to create different adaptive behavior.

Certain cell types in the retina has recently been shown to give robust responses that show a slow decrease in sensitivity due to a decay in membrane potential upon a switch from high contrast to low contrast in their input, which is in fact a change in the opposite direction of the slow component of contrast adaptation. This phenomenon, called sensitization, has been proposed to be generated by inhibitory connections and thus is possibly caused by amacrine level modulation of the contrast adapting circuitry. I use a two pathway model, where an inhibitory connection modulates the dominant excitatory connection, to show how sensitizing responses can be obtained in the retina.

In all the above examples the premise of our approach stays the same: Reduce the apparently complex to simple building blocks that combine using different strategies to produce accurate responses to input stimuli. Then focus on individual building blocks to understand what aspect of the adaptation is controlled by each operation and how they combine to produce the final adaptive behavior. I believe that this approach will help
bridge the gap between understanding the computational aspects of neuronal processing and linking that to biophysical mechanisms.
CHAPTER 2 - LINKING THE COMPUTATIONAL STRUCTURE OF VARIANCE ADAPTATION TO BIOPHYSICAL MECHANISMS

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SUMMARY

In multiple sensory systems, adaptation to the variance of a sensory input changes the sensitivity, kinetics and average response over timescales ranging from < 100 ms to tens of seconds. Here we present a simple biophysically relevant model of retinal contrast adaptation that accurately captures both the membrane potential response and all adaptive properties. The adaptive component of this model is a first-order kinetic process of the type used to describe ion channel gating and synaptic transmission. From the model, we conclude that all adaptive dynamics can be accounted for by depletion of a signaling mechanism, and that variance adaptation can be explained as adaptation to the mean of a rectified signal. The parameters of the model show strong similarity to known properties of bipolar cell synaptic vesicle pools. Diverse types of adaptive properties that implement theoretical principles of efficient coding can be generated by a single type of molecule or synapse with just a few microscopic states.

INTRODUCTION

The range of natural signals exceeds the dynamic range of neurons. As a result, neural circuits adapt so as to more efficiently encode the recent history of inputs. One widespread example of this process occurs in response to a change in the magnitude of
fluctuations, or the variance of a sensory input (Laughlin, 1989). Variance adaptation is known to occur in many sensory systems, including the vertebrate retina and visual cortex, fly visual system, and the avian auditory forebrain (Fairhall et al., 2001; Nagel and Doupe, 2006; Ohzawa et al., 1985; Shapley and Victor, 1978; Smirnakis et al., 1997).

In all of these systems, when the stimulus environment changes from a low to high variance, temporal filtering quickly accelerates, the sensitivity decreases and the average response increases. (Baccus and Meister, 2002; Chander and Chichilnisky, 2001; Kim and Rieke, 2001; Nagel and Doupe, 2006). As the environment maintains a high variance, slow changes occur on the order of 1-10 s that are comprised mostly of a slow homeostatic decay in the average response that opposes the fast change in baseline. (Baccus and Meister, 2002; Fairhall et al., 2001; Nagel and Doupe, 2006). Upon a switch from high to low contrast all these changes reverse direction. The time constants for the slow component of adaptation are asymmetric, with the baseline decaying faster in high contrast than it rises in low contrast. The remarkable similarity of these properties across species and sensory systems indicates a strong commonality in the process of encoding signals that vary in amplitude (Baccus, 2006; Baccus and Meister, 2002; Fairhall et al., 2001; Nagel and Doupe, 2006).

In the vertebrate retina, although all of these adaptive changes are observed widely among ganglion cells and some amacrine cells, there is diversity in the adaptive strategies of different cell populations. For example, Off-type cells change their gain more than On-type cells, and On cells show less of a change in temporal processing (Beaudoin et al., 2008; Chander and Chichilnisky, 2001). Bipolar cells also vary in their adaptive properties, with some cells not adapting, whereas others change only their gain or their
temporal processing, or do not exhibit slow changes in baseline (Baccus and Meister, 2002; Rieke, 2001).

There is also diversity in the potential mechanisms that have been proposed for contrast adaptation in retinal ganglion cells (Demb, 2008). Inactivation of voltage-dependent Na channels in ganglion cells can quickly change the gain (Kim and Rieke, 2003). In addition, a large fraction of adaptation occurs as the signal propagates through the synapse from the bipolar cells to ganglion cells (Beaudoin et al., 2007; Zaghloul et al., 2005). A change in basal vesicle release is proposed to cause the slow component of contrast adaptation, and another calcium related mechanism, such as channel inactivation, might cause fast adaptation (Beaudoin et al., 2008; Demb, 2008; Manookin and Demb, 2006).

Across sensory systems, a substantial difficulty in connecting the apparently complex and diverse phenomena of variance adaptation with the set of potential cellular mechanisms is the lack of a quantitative model that captures both the immediate sensory response and all adaptive properties. Several models have been proposed for visual contrast adaptation (Gaudry and Reinagel, 2007; Mante et al., 2008; Shapley and Victor, 1979), yet these focus on only few aspects of adaptation or use abstract components that do not have a clear connection to potential biophysical mechanisms. In addition, previous efforts to describe the rules of contrast adaptation using a model were only constrained by the firing rate of spiking neurons, and not the membrane potential response.

Here we present a simple theoretical framework that combines aspects of models previously used to capture sensory responses and cellular mechanisms, and use it to
Figure 1. Ganglion cell membrane potential response to changing contrast.

A. Top. Contrast of a randomly flickering stimulus drawn from a Gaussian intensity distribution with a constant mean. Contrast values ranging from 3 – 30 % were presented to the retina for periods of 20 s. Middle. Membrane potential recording lasting 300 s of a ganglion cell responding to the 15 different contrast levels. The inset shows the recording before and after the spikes were removed. Bottom. Expanded segment showing transitions to higher and lower contrast. Colored bars indicate different intervals $H_{early}$, 1-5 s after a step to high contrast, $H_{late}$, 15 - 20 s after a high contrast step, $L_{early}$ and $L_{late}$, defined as similar time intervals after a low contrast step. B. Linear-nonlinear models of different periods corresponding to the times indicated by the colored bars in panel A. The stimulus $s(t)$ is convolved with a linear temporal filter $F_{LN}(t)$ (left) that captures the average temporal filter during the time interval. The result is then passed through a static nonlinearity, $N_{LN}(g)$ (right), that captures the sensitivity (average slope), threshold and offset of the response.
interpret the adaptive behavior of retinal neurons. Our goals were to accurately predict
the intracellular membrane potential across a wide range of contrasts and capture all
adaptive properties with a model that has a natural relationship to biophysical properties.
A further goal was that the model be sufficiently simple to gain insight into how its
mechanics give rise to the multiple properties of adaptation.

RESULTS

We presented to the isolated salamander retina a spatially uniform visual stimulus
that flickered randomly. The intensity changed every 30 ms and was drawn from a
Gaussian distribution with a constant mean to avoid contributions from luminance
adaptation. The temporal contrast also varied randomly by changing the standard
deviation of the distribution every 20 s, with recordings lasting at least 300 s and
containing 15 contrasts (Figure 1A). Under these conditions, inner retinal neurons are
known to adapt to the contrast of the stimulus environment. We recorded the intracellular
membrane potential responses from inner retinal neurons. To isolate the strong
component of adaptation that occurs prior to spiking (Baccus and Meister, 2002; Kim and
Rieke, 2001; Zaghloul et al., 2005), we digitally removed spikes from the recording to
analyze the subthreshold membrane potential.

In addition to capturing the membrane potential, we sought a model that would
quantitatively reproduce the properties of contrast adaptation. These adaptive properties
have been quantified using a linear-nonlinear “LN” model (see methods) consisting of a
linear temporal filter passed through a static nonlinearity. The linear filter represents the
average feature that leads to membrane depolarization, and the nonlinearity represents the
average instantaneous comparison between the filtered visual stimulus and the response.
**Figure 2. The Linear Nonlinear Kinetic (LNK) model.**

A. A train of impulses that changed in amplitude from low to high is shown as an input, $u(t)$ presented to first-order kinetic model with four states. Numbers indicate rate constants for transitions between the resting, $R$, active, $A$, and inactivated states, $I_1$ and $I_2$. The rate constant between the resting and active state is modulated by the amplitude of $u(t)$. The output indicates the occupancy in the active state, $A(t)$.  

B. The LNK model. The input $s(t)$ is first convolved with a linear temporal filter, $F_{LNK}(t)$ and then passed through a static nonlinearity, $N_{LNK}(g)$ that does not change with contrast. The output of the nonlinearity $u(t)$ controls two rate constants in the kinetics block, one that leads to the active state, and one that accelerates recovery from the inactivated state, $I_2$. Other rate constants are fixed, and the output of the model $r'(t)$ is the occupancy of the active state, $A(t)$.  

C. The membrane potential response of an adapting amacrine cell compared to the LNK model output for a transition to low contrast (left) and a transition to high contrast (right).  

D. The LNK model compared to the amacrine cell response for three repeats of an identical stimulus sequence.  

E. The distribution of the absolute difference in membrane potential between responses to an identical stimulus compared to the distribution of the difference between the model output and membrane potential responses. Results are combined for 6 cells with three repeated responses each across the entire recording.
Both quantities are just average measures given a particular set of stimulus statistics, and it is realized that the underlying system is more complex with additional nonlinearities (Baccus and Meister, 2002; Kim and Rieke, 2001). Thus the LN model can reveal and quantify adaptation, but does not produce adaptation itself. When LN models are used to represent different time intervals relative to a contrast step, the most accurate linear filter changes, as does the nonlinearity, indicating the presence of an adaptive response (Figure 1B and 1C). A high contrast step quickly accelerates temporal processing as measured by the time to the first peak of the linear filter, makes the temporal response more differentiating and decreases sensitivity defined as the average slope of the nonlinearity (Demb, 2008). High contrast also quickly produces a depolarizing offset, as measured by the average value of the nonlinearity that then slowly decays away. We then tested a new model to capture both the intracellular membrane potential (Figure 1A) and adaptive properties (Figure 1B and 1C) across multiple contrast levels.

The linear-nonlinear-kinetic model

Many biophysical mechanisms produce changes in gain, including ion channel inactivation, biochemical cascades, receptor desensitization, and synaptic depression (Burrone and Lagnado, 2000; DeVries and Schwartz, 1999; He et al., 2002). A widely used approach to describe these mechanisms uses a first-order kinetic model, whereby a system transitions between different states governed by a set of rate constants (Colquhoun and Hawkes, 1977; Hodgkin and Huxley, 1952). Initially, we sought to capture adaptive properties with a kinetic model, without regard to any one specific corresponding mechanism. A simple example of such a model has four states, shown in
Figure 2A. The first state represents a pool of available molecules or signaling elements in a resting state, $R$, such as closed ion channels or receptors, synaptic vesicles in the readily releasable pool, or an inactive enzyme in a biochemical cascade. The second state is the active state, $A$, which is the output of the system. This state would represent open ion channels or receptors, an active enzyme or neurotransmitter in the synaptic cleft released from vesicles. The third and fourth states $I_1$ and $I_2$ represent inactivated states, such as inactivated ion channels, desensitized receptors, or depleted pools of synaptic vesicles. Each signaling element can occupy one of the states, and the rate of transition between the states is governed by a set of first-order differential equations (see methods). Rate constants are either fixed, or can vary in time by being scaled multiplicatively by an input. The coupling of an input to the system is analogous to a reaction rate that depends on the concentration of the reactants. For example, the change in the active state is described by,

$$\frac{dA}{dt} = \text{inflow} - \text{outflow} = k_a u(t) R(t) - k_{fi} A(t),$$

where $R(t)$ and $A(t)$ are the occupancies of the resting and active states, $k_a$ and $k_{fi}$ are constants, and $u(t)$ is the input that scales the activation rate constant, $k_a$.

When a train of pulses of either small or large amplitude drives the four-state system, the larger input produces output pulses with a smaller gain and generates a positive shift in baseline (Figure 2A). To generate dynamics with both fast and slow timescales as seen in contrast adaptation, the fourth state, $I_2$ couples to the first inactivated state, $I_1$ using slower rate constants. As a result, a slow shift in baseline occurs following a change in the amplitude of the input. The rate constants in the four-state model are the rates of
activation, $k_a$, fast inactivation, $k_{fi}$, fast recovery, $k_{fr}$, slow inactivation, $k_{si}$, and slow recovery, $k_{sr}$.

Although this four-state system can produce adaptive changes in response properties, it still lacks the temporal filtering and selectivity present in retinal neurons. At a fixed mean luminance, photoreceptors are nearly linear. Strong rectification first appears at the level of amacrine and ganglion cells, coinciding with strong contrast adaptation (Baccus and Meister, 2002; Kim and Rieke, 2001; Rieke, 2001). The leading candidate for a strong threshold is voltage dependent calcium channels in the bipolar cell synaptic terminal (Heidelberger and Matthews, 1992), a point that would occur prior to any adaptive changes in sensitivity in the presynaptic terminal or postsynaptic membrane.

Thus, we combined the adaptive system with a linear-nonlinear model, yielding a system with a linear temporal filter, a static nonlinearity, and an adaptive kinetics block (Figure 2B). In this linear-nonlinear-kinetic (LNK) model, the kinetics block contributes both to the overall temporal filtering and sensitivity of the system, making these properties depend on the input. Thus, the linear filter and nonlinearity, $F_{LNK}$ and $N_{LNK}$ of the LNK model are not the same as the filter and nonlinearity, $F_{LN}$ and $N_{LN}$ in an LN model fit to the entire response. To couple the initial linear-nonlinear system to the kinetics block, the output of the nonlinearity, $u(t)$, scales one or two rate constants. Although this means that the rate of transition is proportional to the output of the nonlinearity, a higher order dependence - such as the dependence of vesicle release on a higher power of the calcium concentration – can be captured in the nonlinearity itself.

We fit LNK models using a constrained optimization algorithm (see methods). Briefly, the filter and nonlinearity were reduced to a set of 20 parameters, and the kinetics
Figure 3. The LNK model captures retinal contrast adaptation.

A-B. Linear-nonlinear models were computed for the membrane potential response of a ganglion cell during $H_{\text{early}}$, $H_{\text{late}}$, $L_{\text{early}}$ and $L_{\text{late}}$. LN models were also fit to the output of an LNK model. High contrast was 35 % and low contrast was 8 %. Left. Linear filters, $F_{LN}(t)$ for all of low or high contrast, fit to the recording and LNK model. Right. Static nonlinearity, $N_{LN}(g)$ for all four intervals fit to the recording and LNK model. C. The change in the peak of the linear temporal filter of an LN model fit to the membrane potential response or to the LNK model. Results for C-F are averaged across 12 amacrine and ganglion cells. D. The average sensitivity computed as the average slope of the nonlinearity of an LN model fit to the membrane potential response or to the LNK model as a function of contrast. E. The normalized change in average membrane potential after a contrast switch, compared between a cell’s response and its LNK model. Normalization was performed by subtracting the mean and dividing by the standard deviation of the entire recording. F. The normalized average membrane potential at the end of a contrast period for each cell’s response and its LNK model as a function of contrast.
block contributed an additional 5 parameters. The activation rate $k_a$ was scaled by the input, and most other rate constants were fixed. In addition, to capture the contrast dependence of the rate of slow adaptation, the input scaled the rate of slow recovery $k_{sr}$. The motivation for scaling of the slow rate constant by the input is discussed further below.

**Accuracy of the LNK model**

We compared the LNK model output to the cell’s membrane potential response across the entire 300 second recording spanning 15 contrasts. The model accurately captured the response to contrast transitions, at both decreases and increases in contrast (Figure 2C, Supplemental Figure S1). The correlation coefficient between the model and the response was $88 \pm 4\%$ ($90 \pm 2\%$ for bipolar cells ($n = 5$), $89 \pm 4\%$ for amacrine cells ($n = 9$) and $86 \pm 4\%$ for ganglion cells ($n = 7$)). We then compared these values to the intrinsic variability of each cell by repeating a stimulus sequence two to three times. The accuracy of the model was nearly that of the variability between repeats of the stimulus, which was $90 \pm 5\%$ ($92 \pm 2\%$ for bipolar cells, $92 \pm 4\%$ for amacrine cells, and $89 \pm 6\%$ for ganglion cells). (Figure 2D and 2E). Thus, the LNK model accurately captured the membrane potential response to changing contrast for inner retinal neurons.

**The LNK model captures adaptation**

We then assessed how well the LNK model captured properties of adaptation by fitting LN models to both the data, and to the LNK model. Examining the temporal filters of the LN models, the LNK model captured the fast change in temporal processing between low and high contrast (Figure 3A). In addition, the LNK model captured fast
Figure 4. Internal dynamics of the LNK model.

A. LNK model of an adapting ganglion cell. Colored arrows indicate the output of the different stages shown in panel B, and colors in states correspond to the state occupancies shown in panel B. B. Top to bottom, the output of the linear filter, the output of the nonlinearity and the state occupancies for each of the four states. Left to right, a transition to high contrast, a transition to low contrast, and segments of high and low contrast at an expanded timescale.
changes in sensitivity between low and high contrast as well as fast and slow changes in baseline membrane potential (Figure 3B). Across a population of cells, by examining the time to peak of the LN model linear filter, \( F_{LN} \), the average temporal filtering of the LNK model closely matched that of the cell’s membrane potential response across the full range of contrasts (Figure 3C). In addition, the average overall sensitivity of the LNK model as measured by the average slope of the LN model nonlinearity \( N_{LN} \), closely matched that of the cell’s response across the range of contrasts (Figure 3D). After a transition in contrast, the LNK model matched the change in average membrane potential of a cell across a range of contrast transitions (Figure 3E). Finally, the LNK model matched slow changes in average membrane potential, as the model matched the near steady-state average membrane potential value of a cell reached at the end of 20 s of constant contrast (Figure 3F). Thus, the LNK model accurately captures both the membrane potential response and all adaptive properties of inner retinal neurons.

**How an LNK system adapts to the variance**

Figure 4 illustrates how the dynamics of the LNK model generate variance adaptation. The initial linear filter selects a particular feature of the stimulus. Then, the nonlinearity thresholds the signal, such that when the contrast changes, the output of the nonlinearity changes its standard deviation, but also changes its mean and other statistics. Adaptation is then accomplished by the action of the kinetic model.

When the contrast increases, the input to kinetics block increases its mean signal level, thus increasing the activation rate constant. As a result, the increase in contrast automatically accelerates the response. The resulting increase in the occupancy of the
active state depletes the resting state. We define the gain of the kinetics block as the change in the occupancy of the active state caused by a small change in the input, $\Delta u$.

We derive in the supplemental experimental procedures that $\Delta A$ is simply a product of the input, $\Delta u$, scaled by the rate constant, $k_a$, and the resting state occupancy, $R$,

$$\frac{\Delta A_{\text{net}}}{\Delta u} = k_a R(t) \Delta t. \quad (2)$$

Thus, the instantaneous gain of the kinetics block is proportional to the resting state occupancy. As such, depletion of the resting state decreases the gain (Figure 4B). As the resting state, $R$, depletes, the inactivated states increase in occupancy at different rates. These inactivated states act as a buffer, controlling the occupancy in the resting and active states. In particular, the slow inactivated state, $I_2$, increases gradually, producing the slow offset decay in the active state. At the transition to low contrast, occupancy of $I_2$ slowly decreases as the resting state recovers.

A key function of the first inactivated state $I_1$ was revealed by attempting to fit models using other network topologies. We found that when slow rate constants existed on the return path from the active back to the resting state, the fast and slow kinetics became coupled and it was not possible to accurately produce dynamics with both time scales (Supplemental Figure S2). Thus, state $I_1$ served to generate distinct fast and slow properties. As previously observed, changes in temporal processing occurred quickly, most change in gain occurred at a fast timescale, and changes in offset occurred with both fast and slow timescales (Baccus and Meister, 2002). At a fine timescale (Figure 4B, right), membrane potential responses are asymmetric, having a faster rise rate than decay. The LNK model generates these responses by first producing brief transients as the output of the nonlinearity. These transients are then filtered by a linear combination of
exponentials produced by the kinetics block (see Figure 7), yielding an asymmetric response.

A strict relationship exists between fast and slow offsets, in that the fast and slow offsets oppose each other. In this way, the slow offsets produce a homeostatic regulation of the membrane potential (Baccus and Meister, 2002). This effect can be understood as an action of fast and slow subsystems in the kinetics block. At the transition to high contrast, the increase in the average activation rate constant leads to a fast equilibration among the first three states. This increases the mean occupancy level of both the active and inactivated state $I_1$, and decreases occupancy in the resting state. The increase in the occupancy of $I_1$, however, then leads to a slow equilibration involving the second inactivated state, as $I_2$ slowly steals occupancy from the other states. Thus, the architecture of a fast subsystem linked to a slower reservoir leads to the transient offset, which is then corrected homeostatically towards an intermediate steady state value.

Slow adaptation is temporally asymmetric, such that adaptation to a contrast increase proceeds faster than to a contrast decrease. This property is consistent with known principles of statistical estimation, such that it takes longer to accurately estimate the variance of a distribution when the variance decreases (DeWeese and Zador, 1998). However, this asymmetry did not arise with fixed slow rate constants of inactivation, $k_{si}$ and recovery, $k_{sr}$. To achieve this property, it was necessary to scale the rate constant $k_{sr}$ that controlled the transition between $I_2$ and $I_1$ by the nonlinearity output $u(t)$, such that different contrasts produced slow adaptation with different time constants.

An additional aspect revealed by the model is the average occupancy of each of the states, which is controlled by the rate constants. At all times, around 99% of the total
Figure 5. LNK models of different retinal neurons.

A. LNK model of an Off-type bipolar cell with three kinetic states. B. LNK model of an Off-type transient amacrine cell. C. Two pathway LNK model of an On-Off ganglion cell fit together in a single model. The outputs of the two pathways are summed. For this cell, the relative weighting of the Off pathway was 8.5 times that of the On pathway. D. Rate constants for the kinetics block for different cell types and pathways. Shown are averages for 5 Off bipolar cells, 7 Off pathways from Off or On-Off amacrine cells, 5 Off pathways from Off or On-Off ganglion cells and 12 On pathways from On-Off amacrine or ganglion cells.
A

Bipolar cell

B

Amacrine cell

C

ON-OFF ganglion cell

D

Kinetic rate constants

<table>
<thead>
<tr>
<th></th>
<th>$k_a$</th>
<th>$k_{fi}$</th>
<th>$k_{fr}$</th>
<th>$k_{si}$</th>
<th>$k_{sv}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bipolar</td>
<td>23 ± 9</td>
<td>50 ± 5</td>
<td>87 ± 11</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Amacrine OFF</td>
<td>95 ± 12</td>
<td>8 ± 2</td>
<td>5 ± 1</td>
<td>1.0 ± 0.5</td>
<td>0.03 ± 0.02</td>
</tr>
<tr>
<td>Ganglion OFF</td>
<td>131 ± 20</td>
<td>15 ± 8</td>
<td>48 ± 20</td>
<td>6 ± 3</td>
<td>0.02 ± 0.02</td>
</tr>
<tr>
<td>Amacrine-Ganglion ON</td>
<td>39 ± 7</td>
<td>45 ± 6</td>
<td>1.4 ± 1.8</td>
<td>0.30 ± 0.05</td>
<td>0.002 ± 0.001</td>
</tr>
</tbody>
</table>
occupancy was in the inactivated state, $I_2$. The effect of this is that a small fractional change in $I_2$ results in a larger change in the resting and active states. The biophysical interpretation of this is that if a signal is carried by a molecule or synaptic vesicle, a very large part of the system is unavailable to transmit the signal.

Adaptation in different cell types

Many bipolar cells adapt to contrast, but show changes in gain and kinetics that are smaller than for amacrine or ganglion cells (Baccus and Meister, 2002; Rieke, 2001). Figure 5A shows an LNK model for an adapting bipolar cell. For bipolar cells, we found that the nonlinearity $N_{LNK}$ was placed symmetrically around the mean of the input, meaning that the nonlinearity did not rectify the signal. However, the response of the cell did appear saturated, as negative deflections were larger than positive. This corresponds to saturation in the nonlinearity of an overall LN model $N_{LN}$, as has been observed previously (Baccus and Meister, 2002; Rieke, 2001). This saturation can be explained by the kinetics block producing fast adaptation, such that upon a positive deflection, the gain of the kinetics block quickly drops (Supplemental Figure S3A). Thus, although the saturating response of the cell at high contrast appears to be caused by an instantaneous nonlinear process, it is in fact due to a fast, time-dependent nonlinearity that can be resolved by the parameters of the adaptive kinetics block.

Compared with bipolar cells, transient amacrine cell responses are more rectified, and show greater adaptation to contrast (Baccus and Meister, 2002). Whereas the midpoint of the bipolar cell nonlinearity $N_{LNK}$ was at $7 \pm 5\%$ (n=5) of the input range below the mean, for amacrine and ganglion cells it was on average $26 \pm 2\%$ (n=12) above the mean input (Figure 5B and 5C). In the LNK model, the amacrine cell nonlinearity was shifted to the right, indicating greater thresholding of the response. In
the kinetics block, the path of recovery from the active state back to the resting state ($A$ to $I_1$ to $R$) was slower than for bipolar cells, such that the slowest rate constant was $43.0 \pm 1.8$ ($n = 5$) for bipolar cells, but $5.0 \pm 0.7$ ($n = 12$) for amacrine and ganglion cells. Finally, amacrine and ganglion cells required a second inactive state $I_2$ linked by slow rate constants.

On-Off ganglion cells were fit using a two-pathway LNK model (Figure 5C). The Off pathway was similar to that of adapting Off amacrine cells in its threshold, and kinetic parameters. Compared with the Off pathway, the On pathway had a slower filter, as expected, a higher threshold, and different kinetics. The two pathways with separate initial stimulus features, and independent adaptive properties likely combine to contribute to the multidimensional stimulus sensitivity observable in retinal ganglion cells (Fairhall et al., 2006).

The different cell types, and the On and Off pathways had distinct kinetic parameters (Figure 5D). The precision of these parameter estimates was generally to within 30 %, and is shown in Supplemental Figure S3B for parameters specifying the fast kinetics and the nonlinearity. We then considered how these different parameters give rise to different adaptive behavior.

**Adaptation is controlled by the mean of a rectified signal**

Because all adaptive properties were localized to the kinetics block, we examined in the model which statistics of the internal stimulus representation caused adaptation in the kinetics block. The strongest contrast adaptation arises in some amacrine and ganglion cells. It is also at this level that a strong threshold appears in the response. In fact, from
Figure 6. Variance adaptation is adaptation to the mean of a rectified signal.

A. Top, the nonlinearity output $u(t)$ at low and high contrast. Second – fourth row, $u(t)$ with the mean, standard deviation or skewness held constant, and the other statistics varied as in the control case. B. Gain as a function of contrast with the different statistics held constant, measured as the average occupancy of the resting state, $R(t)$ (from eq. 2).

C. Top, the control nonlinearity output $u(t)$ at low and high contrast. Second – fourth row, $u(t)$ with the mean, standard deviation or skewness varying as in the control case, and with the other statistics held constant. D. Gain as a function of contrast with the different statistics changing alone. Previous work it appears that there is a correspondence between threshold and adaptation, as sustained amacrine cells, which have a more linear response, also show less adaptation than transient amacrine cells (Baccus and Meister, 2002).
Because the nonlinearity changes the statistics of the input, we altered the direct input to the kinetics blocks by taking the nonlinearity output and then changing its mean, standard deviation or skewness. To assess adaptation in each case, we measured the average gain of the kinetics block as the average occupancy of the resting state (from eq. 1).

We first kept constant the mean, standard deviation or skewness, while allowing the other statistics to vary with contrast as in the control conditions. We found that even though the standard deviation or skewness were kept constant, gain changes occurred that were at least as large as in the control condition (Figure 6A and 6B). However, when we kept the mean input constant and allowed other statistics to vary, gain changes were abolished.

Then we changed the mean, standard deviation or skewness, and kept the other statistics constant across contrast. In this case, we found that changing the standard deviation or skewness did not cause adaptation, and in fact produced the opposite effect, causing the gain to increase with increasing standard deviation (Figure 6C and 6D). However, allowing the mean alone to vary caused changes in gain even larger than the control condition.

These results show that changes in the mean input to the kinetics block are both necessary and sufficient to produce adaptation. Thus, a key function of the nonlinearity in generating adaptation is to cause a change in contrast in the stimulus to be transformed into a change in the mean value of the signal. Adaptation to variance can be explained by adaptation to the mean value of a rectified signal.

Thus, from analysis of the model, we propose that bipolar and sustained amacrine and ganglion cells, all which have less of a threshold in their response, experience less
Figure 7. Change in kinetics precedes the change in gain.

A. The impulse response function, $F_k$, of the kinetics block was measured by presenting an impulse added to a low or high baseline, representing the mean output of the nonlinearity at low or high contrast. Top, input to the kinetics block $u(t)$ consisting of brief impulses $\Delta u$ added at different times relative to a change in the baseline value of $u(t)$. Middle, impulse response $F_k(t)$ of kinetics block resulting from $\Delta u$ at different times relative to an increase in $u(t)$. Bottom, $F_k(t)$ at different times relative to decrease in $u(t)$. B. Top, Membrane potential and LNK model of an amacrine cell at a transition from 35 to 5% contrast. Impulses $\Delta u$ were added to the kinetics block input $u(t)$ at different times separated by 10 ms relative to the contrast transition and the resulting filter $F_k(t)$ was computed. Middle, time constant of $F_k(t)$ at different times relative to the change in contrast. This time constant was measured as a single exponential fit to $F_k(t)$. Bottom. Gain measured as the amplitude of $F_k(t)$ at different times relative to the change in contrast. C. For the contrast transition shown in B, small impulses $\Delta s$ were added to the stimulus $s(t)$ and presented to the LNK model at different times separated by 10 ms relative to the contrast transition. The resulting change in the model output $r'(t)$ averaged over many stimulus sequences of $s(t)$ was taken as the impulse response to $\Delta s$. Top. The time to peak of the impulse response to $\Delta s$. Bottom. Amplitude (rms) of the impulse response to $\Delta s$. 
\( u(t) \)

**A**

- \( t = -200 \text{ ms} \)
- \( \tau = 77 \text{ ms} \)
- \( t = 0 \)
- \( \tau = 29 \text{ ms} \)
- \( t = 200 \text{ ms} \)
- \( \tau = 29 \text{ ms} \)

**B**

- \( V_m \) (mV)
- \( \tau \) (ms)
- Time to peak (ms)
- Time to low contrast (s)

**C**

- Data
- Model

\[ u(t) = x_{10^{-3}} - 100 \text{ ms} \]

\[ \tau = 77 \text{ ms} \]

\[ t = -200 \text{ ms} \]

\[ \tau = 29 \text{ ms} \]

\[ t = 0 \]

\[ \tau = 29 \text{ ms} \]

\[ t = 200 \text{ ms} \]

\[ \tau = 76 \text{ ms} \]
adaptation because the output of this threshold changes its mean value less in response to a change in contrast. In comparison, transient amacrine and ganglion cells with a sharp threshold (Figure 5B and 5C) experience greater changes in the mean value of the input to the kinetics block.

**Instantaneous change in kinetics, delayed change in gain**

Fast adaptation consists of nonlinear properties of the response that unfold on a timescale similar to the integration time of the response. To measure fast adaptation, previous studies used LN models computed in small time intervals to assess how adaptation changed the response near a contrast transition (Baccus and Meister, 2002). This approach, however, is limited in its temporal resolution due to the amount of data that can be collected in such small intervals.

In the LNK model, because all adaptive properties are localized to the kinetics block, we assessed how signal transmission of this stage changed at different times during the contrast transition. Because adaptation of the kinetics block is controlled by the mean of the input $u(t)$, we simulated an abrupt change in contrast by producing a step change in $u(t)$. Then we assessed the impulse response of the kinetics block alone, by adding a small incremental impulse $\Delta u$ at different times relative to the step transition. We measured the change in the active state $A_\lambda(t)$ resulting from the added impulse. This change was a decaying exponential whose amplitude and time constant depended on the time relative to the contrast transition (Figure 7A). We found that the average temporal filtering of the kinetics block to an incremental input changed instantaneously at the increase in mean input, whereas the gain lagged several hundred ms.
We then measured changes in the impulse response of the kinetics block generated by visual input presented to the beginning of the model. We chose a segment of data near a contrast transition accurately fit by the model (Figure 7B), and measured the impulse response near the contrast transition by presenting a small $\Delta u$ to the kinetics block at different time points, and then measured the time constant and gain from the resulting change $A_{\Delta}(t)$ in the active state. From the model, we found that both the time constant and instantaneous gain fluctuated quickly in the high contrast environment. Thus, even at a fixed contrast, the gain and temporal filtering change continually depending on the recent input sequence. Although an LN model is a reasonable approximation to inner retinal neurons at a fixed contrast (Chichilnisky, 2001), the LN model fails to capture this ongoing adaptation of the response (Supplemental Figure S4).

Furthermore, because the LNK model accurately captures the response during a contrast transition, we could assess how the overall system changed its gain and temporal processing at a fine resolution relative to the contrast transition. We presented to LNK models small impulses $\Delta s$ at the beginning of the model, added to different sequences of a white noise input at all 10 ms intervals relative to a decrease in contrast, and then measured the resulting incremental response in the active state. We found that the time to peak of the resulting response changed within the integration time of the filter, but that the gain lagged up to twice the integration time of the filter (Figure 7C).

Effects at a contrast transition can be understood in terms of the dynamics of the kinetics block. When the contrast changes, the rate constants of the kinetics block change as soon as the input to the kinetics block increases. This is because the overall temporal filtering of the kinetics block is determined by the eigenvalues of the system (Luenberger,
1979), which are in turn a function of the instantaneous rate constants. After the change in the value of the rate constants, the first state occupancy then shifts to a new level of gain and the baseline membrane potential changes. These secondary changes lag the change in temporal filtering because of the causal relationship between the rate constants and the state occupancies. Thus, in an adaptive system of the type represented in the kinetics block of the model, the gain and baseline response necessarily lag the change in the speed of the response, which places limits on how fast the system can control its gain in response to changing signal amplitude.

**Different parameters generate different behaviors**

To understand how the different parameters of the LNK model generated different adaptive behavior, we first examined a previously described difference in adaptation between Off and On cells. Off cells change both their gain and temporal filtering, whereas On cells change their gain, but have less of a change in temporal filtering (Beaudoin et al., 2008). In the LNK model, compared to the OFF cell model, the ON cell has a slower filter, a higher threshold in its nonlinearity and a different set of rate constants (Figure 5C). To test whether it was the differences in rate constants that yielded the different adaptive behavior, we measured the impulse response function of the kinetics block alone by passing a short impulse, and measuring the resulting output.

Because contrast adaptation in the LNK model can be explained by adaptation in the kinetics block to the mean value of the input (Figure 6), we represented high and low contrast by two different mean values, and then presented impulses riding on the two different baselines. We found that the impulse response of the kinetics block also showed differences between On and Off cells, with On cells showing little change in temporal
Figure 8. Different kinetic parameters give rise to different adaptation properties.

The impulse response function, $F_k$, of the kinetics block was measured by presenting impulses $\Delta u$ added to a constant baseline input $u(t)$, representing the average value of $u(t)$ at low or high contrast in response to a white noise stimulus. A. Left, input to the kinetics block used to measure $F_k$. Middle, a four-state kinetics block from the Off pathway. Right, $F_k$ at low and high contrast, and the high contrast $F_k$ rescaled in amplitude. B. Same as A for a ganglion cell’s On pathway. C. The change in gain of the kinetics block in panel A between low and high contrast as a function of two parameters, fast inactivation, $k_{fi}$ and fast recovery, $k_{fr}$. Both parameters were normalized by the mean activation rate, $k_a$. D. The change in the time constant of $F_k$ at low and high contrast as a function of $k_{fi}/k_a$ and $k_{fr}/k_a$. E. The change in shape of $F_k$ as a function of $k_{fi}/k_a$ and $k_{fr}/k_a$, computed as the area of positive values of $F_k$ divided by the total area between the curve and zero. F. Different parameter values of $k_{fi}/k_a$ and $k_{fr}/k_a$ for different cell types.
filtering (Figure 8A and 8B). Compared to the Off pathway, the model of the On pathway showed differences in the rates of fast inactivation, and fast recovery from inactivation (Figure 5D).

We further explored the space of these two parameters by measuring the impulse response at different contrasts for many different parameter values. Thus, we mapped the effects of the two parameters normalized by the activation rate constant on changes in gain, temporal response, and the biphasic temporal response.

Changes in gain resulted when either fast inactivation, $k_{fi}$, or fast recovery, $k_{fr}$, were slow compared to activation (Figure 8C). This can be understood in terms of the depletion of the resting state as a result of increased activation. When the contrast is high, slow recovery will cause a depletion in the resting state. Considering a simplified three state system, at equilibrium, the inflow and outflow of all states are the same,

$$R_u u_w k_d = A_u k_i = I_u k_r,$$

where $u_w$ is a steady input to the kinetics block. The equilibrium occupancy of the resting state can then be solved as,

$$R_u = \left(1 + u_w c_1\right)^{-1},$$

(3)

where $c_1 = (k_a / k_i + k_a / k_r)$. Thus when either $k_i$ or $k_r$ are small compared to $k_a$, $c_1$ becomes large and weights the effect of the input $u_w$ more heavily. This changes the resting state occupancy and therefore the gain (eq. 2) significantly with contrast. This relationship allows an approximation of the adaptive change in gain to be computed analytically directly from the rate constants of the model (Supplemental Figure S5A).

Changes in the time constant of the temporal filter occurred when fast inactivation $k_{fi}$ was prolonged, but were not affected by the rate constant of fast recovery $k_{fr}$ (Figure
Because of the lack of dependence on $k_f$, we considered a simplified system of three states with no return pathway, \( R \xrightarrow{u_a} A \xrightarrow{k_i} I \). We can derive that the impulse response of this system is a weighted sum of two exponentials (see Supplemental Experimental Procedures), one with a time constant $u_\infty(\sigma)k_a$ that depends on the contrast, and one with time constant $k_i$ that is independent of contrast. The weighting between these two exponentials is set by a constant that depends on the contrast and the inactivation rate, such that when $k_i/k_a$ is small, the variable exponential is weighted more heavily. We can use this understanding to predict the adaptive change in kinetics directly from the rate constants of the model (Supplemental Figure S5B).

Finally, the change in differentiation of the temporal filter was produced primarily by fast recovery, with some dependence on fast inactivation as well (Figure 8E). By comparing the state occupancies to the impulse response $F_k$, we saw that $F_k$ was more biphasic when the increase in the inactivated state $I_i$ exceeded the depletion of the resting state (Supplemental Figure S5C). Consequently, when recovery was slow compared to the steps of activation and inactivation, there was transiently a higher level of inactivation, causing an undershoot in the level of activation. Thus, the three rate constants give flexibility to a system to control its gain and temporal filtering as a function of contrast, although not every behavior is possible with this type of simple system.

We then examined the actual model parameters of different cell types and found that different cells occupied different regions of this parameter space, such that On and Off pathways were distinct from each other, and from bipolar cells (Figure 8F). Bipolar cells,
having a faster \( k_{fi} \) and \( k_{fr} \), showed smaller changes in gain and temporal filtering. Off cells with a slower \( k_{fi} \) showed greater gain changes and changes in the time to peak of their overall temporal filter. On cells with a faster \( k_{fi} \) but slower \( k_{fr} \) showed a substantial gain change, less of a change in the speed of the temporal filter, but a substantial change in the temporal differentiation of the filter. Simple kinetic systems, by choosing different rates of inactivation and recovery, can produce different adaptive behavior.

**Correspondence of kinetic properties with those of synaptic vesicle pools**

A number of potential mechanisms have activity-dependent properties that change their gain, including ion channel inactivation, synaptic depression and receptor desensitization. For AMPA-type glutamate receptors, desensitization and recovery are both rapid (< 20 ms) (DeVries, 2000) and thus could not account for all parameters of the kinetics block. Kainate receptors do a have longer time constant of recovery ( \( \sim 1.5 \) s), but again could not account for the rate constants of slow inactivation and recovery in our model. Desensitization could, however contribute a faster component of adaptation. An extension of the current model that accounted for desensitization would be to add a second kinetics block controlled by the output of the first. An alternative would be to add a third inactive state with input and output from the active state that represented a desensitized receptor.

We examined whether the kinetic parameters of the LNK model correspond to the properties of synaptic vesicle pools. Comparing the parameters of the bipolar cell kinetics block to previously measured parameters of cone photoreceptor synaptic release, under conditions that cause depression of photoreceptor synaptic release, replenishment of vesicles occurs with a time constant of \( \sim 250 \) ms (Rabl et al., 2006). This is substantially
longer than the time constants of the bipolar cell kinetics block, which were < 40 ms. In contrast to bipolar cell synaptic terminals, in the photoreceptor terminal a large fraction of vesicles (~ 85 %) are available for release (Rea et al., 2004). Thus, under the stimulus conditions chosen here, vesicle depletion may not play a major role in bipolar cell contrast adaptation. A postsynaptic mechanism has been proposed for contrast adaptation in bipolar cells that requires a change in intracellular calcium (Rieke, 2001). Although this mechanism is unknown, the kinetic parameters measured here serve as an important quantitative comparison for such candidate mechanisms.

However, we found a different result when comparing the kinetic properties of amacrine and ganglion cells to those of synaptic vesicle pools. Using the terminology of (Rizzoli and Betz, 2005), three pools include a readily-releasable pool (RRP), a recycling pool, and a much larger reserve pool. We found this framework can map directly onto the kinetics states of the LNK model. The resting state, $R$, corresponds to a state where the recycling and RRP are filled, and in the active state, $A$, fusion has occurred. The two inactivated states represent depletion of the two smaller pools. In the inactivated state, $I_1$, the RRP is depleted, and in state $I_2$, the recycling pool that refills the RRP is depleted. The activation rate constant $k_a$ corresponds to the rate of immediate release, and fast inactivation $k_{fi}$ corresponds to the rate of depletion of the RRP. The fast recovery rate constant $k_{fr}$ corresponds to the rate of refilling of the RRP from the recycling pool. The slow inactivation rate constant $k_{si}$ represents the rate of depletion of the recycling pool, and the slow recovery rate constant $k_{sr}$ then represents the rate of recruitment from the reserve pool to the recycling pool.

To test whether the kinetics block parameters corresponded quantitatively to those of
synaptic vesicle pools, we compared the parameters of the On pathway of nine amacrine and ganglion cells, to those properties previously measured of On bipolar cell synaptic release. The rate of maximum release from the RRP depends on the membrane potential, and under physiological conditions is less than 150 s\(^{-1}\). (Burrone and Lagnado, 2000).

Our rate constant of activation, \(k_a\), has a maximum value of 39 s\(^{-1}\) \(\pm\) 7. Using published measurements, this would be generated by a presynaptic depolarization of \(-32\) mV, within the expected physiological range of bipolar cells.

Previously, two fast time constants of release have been measured that differ by a ratio of 4–10, the slower of which is less than 0.5 s (Burrone and Lagnado, 2000). The three fast rate constants of our kinetics block will produce two fast time constants. By applying an impulse to the kinetics block, we found these to be 23.5 ± 4.1 ms and 197.6 ± 37.4 ms, differing by a ratio of 8.4 ± 0.8. The maximum rate constant of refilling of the RRP from the recycling pool has been measured to be 1.3 s\(^{-1}\). Correspondingly, the rate constant of fast recovery, \(k_{fr}\), was found to be 1.4 ± 1.8 s\(^{-1}\), although in our case this rate was fixed, and did not depend on the input. The maximum rate constant of refilling of the recycling pool from the reserve pool has been found to be calcium dependent, and has been measured as 0.0013 (Gomis et al., 1999). Correspondingly, the rate constant of slow recovery, \(k_{sv}\), was input dependent, with a maximum of 0.0018 ± 0.0010 s\(^{-1}\). To compare the rate of depletion of the recycling pool with our rate constant \(k_{si}\), we considered that the ratio of the depletion and refilling rates of the recycling pool (our \(k_{si}\) and \(k_{sv}\), respectively) will control the fractional occupancy of the reserve pool. The reserve pool has been estimated to hold 99.30 % of vesicles (Neves and Lagnado, 1999) (called the
“reservoir”), compared with the 99.14 % ± 0.25 estimated from the fractional occupancy of the kinetic states of the LNK model.

Although the rate constants of the LNK model can span a factor of > 10,000, they nonetheless correspond to previously measured values. Thus, starting directly from measured data of the membrane potential undergoing variance adaptation, the parameters of an accurate adaptive model match the known biophysical properties of synaptic release.

DISCUSSION

We have shown that for a uniform field stimulus, retinal contrast adaptation of the subthreshold potential corresponds closely to a model consisting of a nonadapting linear-nonlinear system followed by an adaptive first order kinetics system. The LNK model accurately captures the membrane potential response, fast changes in kinetics, fast and slow changes in gain, fast and slow changes in offset, temporally asymmetric responses, and asymmetric time constants of adaptation. Since our goal was not only to fit the response, but also to draw general conclusions about how adaptation can be implemented, we chose an adaptive component that has a strong correspondence to biophysical mechanisms. This allowed us to use the model to explain how each adaptive property can be produced by a single simple system.

Retinal ganglion cells were modeled using one or two parallel pathways, each with a single LNK stage. However, since bipolar, amacrine and ganglion cell show adaptation, a more accurate circuit model would consist of two sequential LNK stages, and parallel pathways to include amacrine transmission. Why does only a single LNK stage accurately capture ganglion cell responses? Compared to the strong adaptation of
ganglion cells, bipolar cell contrast adaptation to a uniform field stimulus is weak in the intact retina (Baccus and Meister, 2002), as opposed to the stronger adaptation in bipolar cells generated by stronger input when much of inhibitory surround is removed in a slice preparation (Rieke, 2001). If this first adaptive stage is missing in a model, then the input to the second stage will have a greater change in variance across contrasts. But this change in variance will be reduced by the stronger adaptation in the retinal ganglion cell stage, such that in the model, strong adaptation in the kinetics block will compensate for the absence of a weak initial adapting stage. For amacrine cells, it is likely that uniform field stimuli reduce the complexity of adaptive parallel pathways, and that additional adaptive pathways will be needed for more complex stimuli. Amacrine cells that have a similar response properties to their target ganglion cells (Baccus et al., 2008) may be accounted for by a single model pathway that represents the combined parallel effects of excitation and inhibition.

**Components of the LNK model**

In the model, the linear filter conveys a first approximation of the stimulus feature encoded by the cell, and the nonlinearity conveys the strength of that feature. We chose the filtering stage to have a single stimulus dimension as it represents the more simple processing at the level of the photoreceptor or bipolar cell soma, as opposed to a multidimensional feature space as can be found in retinal ganglion cells (Fairhall et al., 2006). The filter has a less direct correspondence to a biophysical mechanism, representing the combining effect of signal transduction, membrane and synaptic properties. For the nonlinearity, it is expected that a major contributor is the voltage dependence of calcium channels. These are, in fact, not instantaneous, although their
kinetics can be sub-millisecond (Mennerick and Matthews, 1996), and thus are effectively instantaneous at the timescale that we are modeling. A more biophysical model would also translate this approximation into a kinetic model.

Previous studies have shown that neurons that exhibit contrast adaptation typically also have a strong threshold (Baccus and Meister, 2002; Chander and Chichilnisky, 2001; Kim and Rieke, 2001). One role of this threshold may be to reject internal noise, (Field and Rieke, 2002; Kastner, 2011) although we have not tested this here. Because adaptation in the kinetics block is primarily sensitive to the mean of the signal input, we find an important key role for the threshold nonlinearity in transforming the variance of the input to the mean level of the signal. Furthermore, because thresholds are common in the nervous system, it is highly likely that a signal with changing variance will be transformed to a signal with a changing mean, giving rise to the commonly observed properties of variance adaptation.

Previous results indicate that adaptation to statistics beyond the mean luminance are controlled primarily by the standard deviation (Bonin et al., 2006). Our finding that contrast adaptation is controlled by the mean value of an internal variable is not in conflict with this result. Because the initial filter combines multiple samples from the stimulus, due to the central limit theorem this will reduce the effects of higher-order moments of the stimulus, making the filtered stimulus more Gaussian. Thus, the standard deviation of the stimulus will have the largest control over the mean of the signal after it then passes through the threshold nonlinearity.

A key feature in the kinetic scheme that controls adaptation is the return path from active to resting states ($A$ to $I_1$ to $R$). If the recovery path from the active state is
considerably slower than the activation path, this leads to depletion of the resting state upon a large input, and therefore a reduction in gain. Thus, by controlling the relative rates of activation and recovery, different adaptive properties can be generated (Figure 8). Although Off cells had a faster response and filter than On cells, Off cells have a proportionally slower rate of fast inactivation, \( k_f \), (relative to the activation rate, \( k_a \)) giving them greater adaptive changes in gain.

In the LNK model, changes in the timescale of slow adaptation are produced by the variable rate constant of slow recovery \( k_s \), which we found to be proportional to the contrast. It has been shown that this timescale of adaptation can change to match the timescale of changes in the stimulus contrast (Wark et al., 2009), although in our studies we used a fixed time interval. Such plasticity of adaptive timescale would not automatically occur in our current model, as such behavior would require that \( k_s \) change with slower dynamics when the contrast changes. If, as we propose, changes in \( k_s \) reflects the calcium dependence of slow vesicle mobility (Gomis et al., 1999), this would predict that these mechanisms reflect an inference about the recent timescale of changes in stimulus contrast.

**Sites of luminance and contrast adaptation**

Our stimuli had a constant mean intensity, and thus do not account for any effects of luminance adaptation, which appears to be independent from contrast adaptation (Mante et al., 2005). Considering the source of this independence, we observed that the initial linear filter for amacrine and ganglion cells was strongly biphasic, such that it transmitted little information about the mean light intensity. Thus, we would expect that most adaptation to luminance occurs at an earlier stage, whereas adaptation to contrast would
occur at a different site, only after the threshold nonlinearity. However, at lower luminance the filter of bipolar cells is more monophasic, transmitting more information about the mean luminance (Burkhardt et al., 2007). Accordingly, in the primate cone pathway, at low intensities the bipolar cell terminal does adapt to the mean luminance (Dunn et al., 2007). Thus it is expected that at lower luminance, mean and luminance adaptation both occur at the same site in bipolar cell terminals. Because our results indicate that adaptation to variance at the bipolar cell terminal is based on the mean signal, adaptation to the mean and contrast of the stimulus may interact at lower luminance.

**Modulation vs. intrinsic adaptation**

Adaptive changes in a neural code can be produced, in principle, by a parallel pathway that measures a statistic and then modulates a second pathway (Mante et al., 2008). Modulatory changes in gain have been shown to arise from peripheral inhibition, and can generate selectivity for differential motion (Cook and McReynolds, 1998; Olveczky et al., 2003). Parallel pathways have flexibility, in that the stimulus statistics that cause adaptation can be different from that encoded by the immediate response of the cell. This organization, however, requires additional neural circuitry to generate adaptation. In contrast, adaptive properties at short timescales in the fly visual system have been captured by a more computational multiple pathway model that produces adaptation as an intrinsic aspect of motion detection (Borst et al., 2005).

Here we find that all properties of retinal contrast adaptation are explained by a model with no such parallel pathway. Instead, transmission of the signal is naturally coupled to an intrinsic adaptation of the response, such that the process of transmitting a
signal changes the rate of that transmission and depletes a store of that signal, leading to a change in temporal filtering, gain and offset. Like adaptation to the mean luminance in the photoreceptor transduction cascade, retinal contrast adaptation corresponds to a model of intrinsic adaptation.

**Relationship to other models**

Other models of contrast adaptation have produced adaptive changes in sensitivity by a feedback pathway that subtracts a filtered version of the output signal (Gaudry and Reinagel, 2007; Victor, 1987). The LNK model differs in that the reduction of sensitivity is produced not by a feedback inhibitory pathway, but by depleting a signal as it is transmitted. In the present model, the return loop represents not a pathway of transmission that reduces the signal, but a state transition that replenishes the available signal. This architecture avoids the need for a feedback inhibitory pathway.

Integrate-and-fire (IF) type models qualitatively cause adaptive gain changes and small changes in temporal filtering (Gaudry and Reinagel, 2007; Keat et al., 2001; Pillow et al., 2005; Rudd and Brown, 1997). By comparison, the LNK model captures both neural responses and all adaptive properties across multiple contrasts, in particular full changes in kinetics, and homeostatic fast and slow changes in response amplitude. For models of the IF type, each spike subtracts an afterpotential, causing refractoriness. However, large afterhyperpolarizations are not observed in retinal data following spiking (Kim and Rieke, 2001), and it is not clear how such a mechanism would cause adaptation measured in the subthreshold potential. Such integrate-and-fire models can show similar behavior to kinetic models (Jolivet et al., 2004), and thus could provide a useful approximation for comparison to models with more direct biophysical significance.
The attraction of simple kinetic systems is that they are both amenable to analytic solutions and simulation, and have a correspondence with biophysical mechanisms. The adaptive properties of kinetic models that represent biochemical processes including neurotransmitter receptors have recently been analyzed from a theoretical point of view (Friedlander and Brenner, 2009). This previous work showed that first order kinetic systems similar to the type discussed here can change their gain when receptors become unavailable with a time course controlled by the rate constants of the kinetic system. We extend these theoretical results to show how changes in temporal filtering and offset can also result from these simple systems. Other theoretical work has considered biochemical networks of two-state systems, analogous to an enzyme with two different conformations, to achieve changes in gain (Ma et al., 2009). This study concluded that at least three such two-state systems are needed to produce adaptation. The system we have considered has fewer overall states, but requires a signaling mechanism with at least three states. Our results highlight the greater adaptive power of molecules with at least three states, such as desensitizing receptors or inactivating ion channels.

**Towards further stages of adaptation and natural vision**

In a step towards understanding adaptation in natural scenes, the use of full field stimuli likely reduces the complexity of adaptive behavior, in that cells in our study could be fit by one or two LNK pathways. More complex spatio-temporal stimuli will undoubtedly require additional adapting pathways, such as adaptation to differential motion and spatio-temporal patterns (Hosoya et al., 2005; Olveczky et al., 2007). In a simple extension of these results, pathways represented by different interneurons would adapt independently. In each pathway, a spatio-temporal filter would define the scale of
adaptation (Mante et al., 2008), and separate thresholds and kinetics blocks would define the adaptive dynamics. A more complex possibility involves feedback between pathways, or plasticity that depends on correlations between cells (Hosoya et al., 2005).

Studying the subthreshold potential allowed us to isolate our analysis from other mechanisms shown to play a role in the transformation from membrane potential to spikes, such as inactivation in Na+ and K+ channels (Kim and Rieke, 2003; Weick and Demb, 2011). Because of the well explored relationship between ion channel properties and kinetic models, incorporating this additional stage of adaptation would then involve adding another kinetic stage representing inactivating ion channels. At each sequential stage, an important direction to extend these results will be to match kinetic parameters of adaptation with kinetic parameters of biophysical mechanisms.

**Theoretical explanations for biophysical properties**

Variance adaptation embodies several theoretical principles of efficient coding previously studied using principles of optimality and information theory. The change in gain allows a cell to use its dynamic range more efficiently (Laughlin, 1989). A change in temporal filtering and biphasic response helps to increase the integration time in an environment of weaker, and therefore noisier signals (Atick, 1992; Van Hateren, 1993). Slow adaptation sets the timescale over which the statistics of the stimulus are measured (Wark et al., 2009). The temporal asymmetry between adaptation to low and high contrast corresponds to a statistical limitation in how fast the variance of a distribution can be measured (DeWeese and Zador, 1998). The LNK model shows how all of these adaptive principles can be implemented by microscopic transitions common to many biophysical mechanisms. Furthermore, the model establishes a correspondence between
adaptation and depletion mechanisms that cause a signaling element to become temporarily inactivated upon its use. Because such depletion mechanisms are prevalent in the nervous system, this may reflect the widespread advantage for each signal to adapt to its own strength.

The parameters of the adaptive block of the LNK model bear great similarity to previously measured parameters of vesicle pools in the bipolar cell ribbon synapse. The correspondence of the LNK model to both adaptive computations and synaptic properties allows us to propose computational explanations for biophysical properties that have previously been measured, but with unknown functional benefits. The small number of vesicles in the readily releasable pool may be required so that release of few vesicles leads to a large change in gain. The rate constants of depletion and refilling of the readily releasable pool may be differentially regulated in different cells so as to control adaptive changes in gain, kinetics or temporal differentiation. Because we find that the inactivated state $I_1$ is needed to produce fast and slow subsystems with different adaptive effects, the presence of the recycling pool may be necessary so that the effects of fast and slow adaptation are decoupled. The dominance of vesicles in the reserve pool may be a natural consequence of slow adaptation, and is necessary for the system to adapt over a sufficient timescale to measure the mean value of the synaptic input. The calcium dependence of the rate of recruitment from the reserve pool may reflect the statistical need to adapt over a longer time interval when the signal is weak. Thus, by making explicit the rules governing both the immediate light response and its adaptation over multiple time scales, we gain insight into how mechanisms can implement an adaptive neural code.
EXPERIMENTAL PROCEDURES & METHODS

Electrophysiology. The intact salamander retina was held in place under a transparent dialysis membrane containing several 150 – 300 µm holes. Intracellular electrodes filled with 2 M potassium acetate (200 – 300 MΩ) were guided into the retina under infrared illumination viewed through a CCD camera. Bipolar cells, adapting transient amacrine cells and ganglion cells were identified by their flash response, receptive field size, and level in the retina. Intracellular recordings were made from 7 bipolar cells, 9 amacrine cells, and 7 ganglion cells. Recordings ranged from 10 - 90 minutes in duration.

Visual Stimulation. A spatially uniform visual stimulus was projected from a video monitor onto the retina. A new stimulus intensity was chosen every 30 ms from a Gaussian probability distribution with mean intensity, $M$ (~ 8 mW/m$^2$) and standard deviation $W$ (Smirnakis et al., 1997). Contrast was defined as $W/M$, and was changed every 20 s to a value between 0.05 and 0.35 drawn randomly from a uniform distribution. The stimulus lasted 300 s (15 contrast levels) and the identical stimulus sequence was repeated at least two times.

LN model calculation. LN models were computed as described (Baccus and Meister, 2002). The stimulus intensity $s(t)$ was normalized to have zero mean, and a standard deviation equal to the contrast. The filter, $F_{LN}(t)$, was computed as the correlation between $s(t)$ and the response $r(t)$ normalized by the autocorrelation of the stimulus. The filter was computed as,

$$F_{LN}(\omega) = \frac{\langle \hat{s}^*(\omega) \hat{r}(\omega) \rangle}{\langle \hat{s}^*(\omega) \hat{s}(\omega) \rangle}$$  

(4)
where \( \tilde{s}(\omega) \) is the Fourier transform of \( s(t) \), \( \tilde{s}^*(\omega) \) its complex conjugate, and \( \langle \ldots \rangle \) denotes averaging over 1 s segments spaced every 0.1 s throughout the recording. The denominator corrects for deviations of the video monitor from a white spectrum (Hunter and Korenberg, 1986). This calculation was performed separately in various time windows surrounding the contrast switch, defined in Figure 1A. The stimulus was convolved with the filter, by computing \( g(t) \),

\[
g(t) = \int F_{LN}(t - \tau) s(\tau) d\tau
\]

The filter was normalized in amplitude so that the variance of \( g(t) \) and \( s(t) \) were equal,

\[
\int s^2(\tau) d\tau = \int g^2(\tau) d\tau
\]

Then, the fixed nonlinearity \( N_{LN}(g) \) was calculated by averaging the values of \( r(t) \) over bins of \( g(t) \). Finally, the prediction of the LN model was calculated as

\[
r'(t) = N_{LN}(g(t)) = N_{LN}\left( \int F_{LN}(t - \tau) s(\tau) d\tau \right)
\]

Because of the normalization of the amplitude of the filter, \( F_{LN}(t) \) summarizes temporal processing, and \( N(g) \) captures the sensitivity to the stimulus.

Linear Nonlinear Kinetic model. The stimulus, \( s(t) \), was passed through a linear temporal filter, \( F_{LNK}(t) \) and a static nonlinearity, \( N_{LNK}(g) \),

\[
u(t) = N_{LNK}\left( \int F_{LNK}(t - \tau) s(\tau) d\tau \right).
\]

This is identical to an LN model, except that the filter and nonlinearity are different functions. The kinetics block of the model is a Markov process defined by

\[
\frac{dP^r(t)}{dt} = P^r(t)Q(u),
\]
where \( \mathbf{P}(t) \) is a column vector of \( m \) fractional state occupancies such that \( \sum P_i = 1 \), and \( \mathbf{Q} \) is an \( m \times m \) transition matrix containing the rate constants \( Q_{ij} \) that control the transitions between states \( i \) and \( j \), with \( Q_{ii} = -\sum_{i \neq j} Q_{ij} \). After this differential equation was solved numerically, the output of the model, \( r'(t) \) was equal to one of the state occupancies scaled to a response in millivolts,

\[
r'(t) = P_2(t) c + d ,
\]

where \( c \) and \( d \) are a scaling and offset term for the entire recording.

States and rate constants are defined as,

\[
\begin{align*}
P_1 &= R \quad & \text{Resting} & \quad Q_{12} &= u(t) k_a \quad & \text{Activation} \\
P_2 &= A \quad & \text{Active} & \quad Q_{23} &= k_{fi} \quad & \text{Fast inactivation} \\
P_3 &= I_1 \quad & \text{Inactivated} & \quad Q_{31} &= k_{fr} \quad & \text{Fast recovery} \\
P_4 &= I_2 \quad & \text{Inactivated} & \quad Q_{34} &= k_{si} \quad & \text{Slow inactivation} \\
Q_{43} &= u(t) k_{sr} \quad & \text{Slow recovery}
\end{align*}
\]

The four state version of this model was,

\[
\frac{d\mathbf{P}(t)}{dt} = \mathbf{P}(t) \begin{pmatrix}
-u(t) k_a & u(t) k_a & 0 & 0 \\
0 & -k_{fi} & k_{fi} & 0 \\
k_{fr} & 0 & -(k_{fr} + k_{si}) & k_{si} \\
0 & 0 & u(t) k_{sr} & -u(t) k_{sr}
\end{pmatrix} .
\]

Some rate constants set to zero were initially allowed to vary in early fits, but their optimal values were found to be near zero. Setting them to zero did not change the
accuracy of optimization but did improve the speed of convergence of the model. For three state models of bipolar cells, \( P(t) = k_s = k_r = 0 \).

Model parameterization. To parameterize the model for fitting, the filter \( F_{\text{LNK}} \) was defined as a sum of orthonormal basis functions

\[
F_{\text{LNK}}(t) = \sum_{j=1}^{15} \alpha_j f_j(t + \delta),
\]  

(13)

where \( \alpha_j \) are the weighting coefficients and \( \delta \) is a single delay parameter for each cell that ranged between 0 and 2 ms. The basis functions were decaying sinusoids of increasing frequency

\[
f_j(t) = \begin{cases} 
\sin \left( \pi j \left( \frac{2t}{\tau} - \left( \frac{t}{\tau} \right)^2 \right) \right) & 0 \leq t \leq \tau \\
0 & t > \tau 
\end{cases}
\]

(14)

with \( \tau \) equal to 1 s and were orthogonalized according to (Keat et al., 2001).

The nonlinearity was a sigmoid function parameterized as:

\[
N_{\text{LNK}}(x) = a \text{erf}(x+1)b_1 + b_2
\]

(15)

where \( \text{erf}(x) \) is the error function defined for cumulative Gaussian distributions, \( a, b_1 \) and \( b_2 \) are parameters of the model, and \( \kappa \) was a constant equivalent to the overall variance of the filtered stimulus \( g(t) \). The exponent of \( a \) varies between zero and twenty, and the activation rate constant \( k_a \) in the denominator scales the nonlinearity so that its maximum is one. Thus, the output of the nonlinearity, \( u(t) \), scales the activation rate in the kinetics block between zero and \( k_a \).
For On-Off ganglion cells, two parallel LNK pathways were used with the outputs of each computed as explained above. The outputs were then scaled with independent weights \( w_{ON} \) and \( w_{OFF} \) and summed to give the final output of the model. The total number of parameters for the model excluding the rate constants set to 0 was 26 for a single pathway and 51 for two parallel pathways.

For numerical integration, a time step of one ms was used for numerical simulation to compute the output of the model. To solve the differential equation for the kinetics block, a discrete-time approximation was used where

\[
e^{Q\Delta t} = I + Q\Delta t
\]  

for matrix \( Q \) and a small \( \Delta t \). Additional details about the fitting procedure can be found in Supplemental Experimental Procedures.

**SUPPLEMENTAL EXPERIMENTAL PROCEDURES**

**Derivation of instantaneous gain**

We define the instantaneous gain of the kinetics block as the incremental change in the active state, \( A(t) \), produced by an incremental change in the input \( u(t) \),

\[
\text{gain} = \frac{\Delta A}{\Delta u}
\]  

(17)

To compute the gain, we consider the difference between \( \Delta A \) produced by \( u(t) \) alone, and produced by \( u(t) + \Delta u \),

\[
\frac{\Delta A_{u(t)}}{\Delta t} = k_a u(t)R(t) - k_f A(t)
\]  

(18)

\[
\frac{\Delta A_{u(t)+\Delta u}}{\Delta t} = k_a (u(t) + \Delta u)R(t) - k_f A(t).
\]

Taking the difference yields the gain
\[ \frac{\Delta A_u}{\Delta u} = k_a R(t) \Delta t, \quad (19) \]

indicating that because \( k_a \) is constant, the gain is proportional to the resting state occupancy \( R(t) \).

**Derivation of adaptive changes in temporal filtering**

Given that contrast adaptation depends largely on the mean input to the kinetics block, we examined the effects of an incremental input \( \Delta u \) that is applied on a background of different mean inputs \( u_\infty(\sigma) \), which represent a steady input that occurs at a given contrast, \( \sigma \). Because adaptation changes the kinetics quickly, we consider the effects of a three state system \( \{R,A,I\} \) that produces only fast adaptation. Furthermore, because we find empirically that adaptive changes in the time to peak do not depend on the recovery rate constant \( k_r \) from the inactive to resting states (Figure 8D), we analyzed a three state system where \( k_r = 0 \),

\[
R \xrightarrow{uk_a} A \xrightarrow{k_i} I. \quad (20)
\]

We consider the incremental effects \( R_\Delta(t) \), \( A_\Delta(t) \) and \( I_\Delta(t) \) on the state occupancies \( R(t) \), \( A(t) \) \( I_1(t) \) produced by a small input \( \Delta \). The impulse response from this input is the combined effect of two initial conditions, one with \( R \cdot \Delta \) added to the active state, and one with \( R \cdot \Delta \) subtracted from the resting state. If we define the magnitude of \( R \cdot \Delta \) to be one, then given the initial condition of

\[
\{R_\Delta, A_\Delta, I_\Delta\}_{t=0} = \{0,1,0\}, \quad (21)
\]

the incremental effect on the resting state remains at zero, and the effect on the active state follows the time course.
\[ A_{\Delta^+}(t) = e^{-k_{\beta}t}. \]  

(22)

Given the second initial condition of

\[ \{R_{\Delta^-}, A_{\Delta^-}, I_{\Delta^-}\}_{t=0} = \{-1, 0, 0\}, \]  

(23)

the resting and active states decay as follows,

\[ R_{\Delta^-}(t) = -e^{-k_{\beta}u_{\infty}(\sigma)t}, \]  

(24)

\[ A_{\Delta^-}(t) = c_2\left(e^{-k_{\beta}u_{\infty}(\sigma)t} - e^{-k_{\beta}t}\right), \]

where \( u_{\infty}(\sigma) \) is the mean input to the kinetics block generated by a constant contrast, \( \sigma \).

The time constant for the incremental response of \( R_{\Delta^-}(t) \) and \( A_{\Delta^-}(t) \) are thus a function of contrast. For the active state response, \( c_2 \) is a constant. Adding eqs. 22 and 24 for \( A_{\Delta^+}(t) \) and \( A_{\Delta^-}(t) \) results in

\[ A_{\Delta}(t) = A_{\Delta^+}(t) + A_{\Delta^-}(t) = c_2 e^{-k_{\beta}u_{\infty}(\sigma)t} + (1 - c_2)e^{-k_{\beta}t}. \]  

(25)

Thus, the combined effects of the incremental change is a weighted sum of two exponentials, one with a time constant \( k_{\beta}u_{\infty}(\sigma) \) that depends on the contrast, and one with time constant \( k_{\beta} \) that is independent of contrast. The constant \( c_2 \) controls whether the kinetics depend on the contrast or not. To solve for \( c_2 \), we combine the equations for \( A_{\Delta^-}(t) \) and \( R_{\Delta^-}(t) \) (eq. 24) into

\[ \frac{dA}{dt} = k_{\alpha} R(t) - k_{\beta} A(t), \]  

(26)

and use the fact that \( u_{\infty}(\sigma) \) is a constant to give the result

\[ c_2 = \frac{u_{\infty}(\sigma)}{u_{\infty}(\sigma) - \frac{k_{\beta}}{k_{\alpha}}}. \]  

(27)
Thus, when the magnitude of $k_i/k_a$ is small, $c_2$ approaches one, and weights the variable exponential in eq. 25 more heavily, causing the kinetics of $A_3(t)$ to depend on contrast.

**Initial guess and optimization of the LNK model**

Optimization was done in MATLAB using the function *fmincon*. Since the explicit expression for the error was not available, approximate gradient and Hessian values were used in either an active set or an interior-point algorithm to minimize the given error measure. The only constraints used were boundary constraints for the parameters, which were for the rate constants to be positive, and the slow recovery rate constant $k_s$ to be slower than 1 s. Because there is no explicit formulation for the error surface, the optimum values obtained are assumed to be non-unique and local. To address this issue, we used using multiple initial points to converge to different optima and then chose the best solution. Further analysis of the error surface in the neighborhood of the optimal solution is described in the section below.

Initial values for the parameters for the linear filter, $F_{LNK}$ and nonlinearity, $N_{LNK}$ were chosen using the LN model for the high contrast period. Rate constants were chosen randomly between [0,100]. For ON-OFF cells, a principal component analysis was used to obtain the first two stimulus directions for which the cell was most sensitive, (Geffen et al., 2007) and these directions were taken as initial filter estimates. In some cases, we used parameters from previously fit cells as an initial condition. This procedure did not affect the result, but improved the speed of convergence.

To avoid any over-fitting of parameters to the finite dataset, a k-fold cross validation method was used. The data was divided into 5 equal length sets consisting of 300 ms
length segments interleaved every 1.5 s. The model was optimized using four of these sets and tested on the fifth. The procedure was then repeated leaving out each of the five sets, and stated correlation coefficient values are the average of the results.

**Error metric**

We desired an error metric that would cause the model to fit all segments of the data. However, at different contrasts, the membrane potential shows substantial variation in its amplitude. Thus, using the mean squared error as an error metric would bias the model towards fitting the high contrast segment of the response. In addition, certain segments of the data contain a larger fraction of power in lower frequencies caused by slow shifts in the baseline membrane potential. Thus it was also necessary that the error metric cause the model to capture both slow shifts in potential and higher frequency fluctuations. In order to address this problem we divided the data into both time and frequency bins, and normalized the error by the standard deviation in each bin. We computed the error measure by first dividing the membrane potential recording \( r(t) \) into 10 s time bins, and then filtered each bin in the frequency domain with discrete filters to yield the response, \( r_{ij}(t,\omega) \), binned over time interval \( i \) and frequency bandwidth \( j \). In practice, only two frequency bins were needed, separated by a cutoff frequency of 4 Hz that divided the response into two bins with approximately equal power. We then computed the error across time and frequency bins as,

\[
E = \sum_i \sum_j \frac{\| r_{ij}(t,\omega) - r'_{ij}(t,\omega) \|}{\sigma_{ij}}
\]  

(28)
where $\sigma_y$ is the standard deviation of the response and $r'_y (t, \omega)$ is the model output for time bin $i$ and frequency bin $j$. This measure normalized the error in different time bins and frequency components so that no one segment dominated the fitting procedure.

**Sensitivity to parameters**

As mentioned above, since the error surface was known to be non-convex, and the obtained optimum solutions local, we tested the sensitivity to parameters in the vicinity of the optimum solutions. Furthermore, we observed whether other parameters could compensate for the increase in error observed after perturbing a single parameter from its optimum value.

To measure the sensitivity of the model to individual parameters, we perturbed five of the parameters of the nonlinearity and kinetics block one at a time from their optimum values and held the parameter constant at the perturbed value (Supplemental Figure 3B). Without allowing any other change in the remaining parameters, we calculated the percentage deviation from the optimum error value. To measure how much the other parameters could compensate for this deviation, the rest of the parameters were reoptimized, and another error value was computed from this new set of parameter values.
CHAPTER 3 - ADAPTIVE CHANGES FROM MULTIPLE RETINAL PATHWAYS

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ABSTRACT

Sensory neurons change their preferred stimulus feature based on the statistics of their recent input. A widespread example of this adaptive process occurs when the strength of the input causes a change in temporal filtering. In the visual system, in an environment of high luminance or contrast, cells become more temporally differentiating, emphasizing changes in intensity. This process improves the efficiency of information transmission by reducing correlations when the noise is lower. This behavior is produced by nonlinear dynamics of the system, making it a challenge to understand how this computation is generated. Here we investigate adaptive temporal differentiation to contrast in On-Off amacrine and ganglion cells of the salamander retina. To analyze the source of this adaptation, we use a novel biophysically relevant model with two pathways each consisting of a linear temporal filter, a threshold nonlinearity and an adaptive first-order kinetic system. This linear-nonlinear-kinetic (LNK) model captures all adaptive properties and the membrane potential response in an environment of changing contrast. We find that an increase in contrast changes the relative contribution of the On and Off pathways, yielding a more differentiating overall response. Most of this change arises from differences in the threshold of the two pathways. Although each pathway adapts,
their independent adaptive properties make only a minor contribution to changes in temporal differentiation. We conclude that adaptive temporal differentiation in the retina has a distinct source from other temporal contrast adaptation, and explain this computation as arising from differential nonlinear properties in parallel neural pathways. In addition, we show how a two-pathway LNK model can capture a novel form of adaptive plasticity in the retina known as sensitization, which elevates the sensitivity of a neuron following a high contrast stimulus.

**INTRODUCTION**

The ensemble of sensory inputs encoded by a neuron varies with the environment. Many sensory environments are composed of strong signals, including high luminance, high contrast, fast velocity or loud auditory stimuli. In each of these cases, in order to use a cell’s dynamic range more efficiently, sensory neurons adapt to the strong stimulus by decreasing their sensitivity (Fairhall et al., 2001; Laughlin, 1989; Nagel and Doupe, 2006; Shapley and Victor, 1978).

A second prominent aspect of adaptation to changes in stimulus strength involves a change in the preferred stimulus feature. Natural signals contain a larger fraction of low temporal frequencies, and thus nearby points in time have similar intensity. As such, when the signal-to-noise ratio (SNR) is low, it becomes more efficient to discard weaker and noisier high frequency signals, averaging over the noise across a longer time interval. At high SNR, however, cells can take advantage of the less noisy environment to reduce correlations in the input, and thus the temporal response becomes faster and more differentiating (Atick, 1992; Baccus, 2006; Baccus and Meister, 2002; Nagel and Doupe, 2006; Singh and Theunissen, 2003; Van Hateren, 1993). These arguments have also been
applied to changing spatial receptive fields, explaining why during low luminance, receptive field centers are larger and surrounds are weaker. (Atick, 1992; Barlow et al., 1957; De Valois et al., 1974; Enroth-Cugell and Robson, 1966; Van Hateren, 1993)

Here we study the change in temporal differentiation with changing temporal contrast in the vertebrate retina (Baccus and Meister, 2002; Beaudoin et al., 2007; Shapley and Victor, 1978), which also occurs in human perception (Stromeyer and Martini, 2003). Although this process has been described quantitatively, and its functional importance is understood, how this change in temporal bandwidth is generated within the retinal circuit is not well described. One obstacle to this understanding is that the process by definition involves nonlinear dynamic properties of the system. A second complication is that signals in the retina are merged through multiple neural pathways, each potentially with its own adaptive properties.

Recently, we have developed a computational model to capture the adaptive properties of a cell to an environment of changing contrast. This model consists of a cascade of three blocks—a linear temporal filter, a time-independent or static nonlinearity that applies a threshold and saturation to the input, and a first-order kinetic system that creates the dynamic adaptive changes in response to changing input statistics. This linear-nonlinear-kinetic model (LNK) captures all adaptive properties in an environment of changing contrast as well as the membrane potential response nearly to within the variability of the cell (Ozuysal & Baccus, submitted). The kinetic system bears similarity to properties of synaptic vesicle pools.

Here we analyze On-Off amacrine and ganglion cells, which we find to have strong adaptive changes in temporal differentiation with contrast. Using pharmacology and a
two-pathway LNK model, we assess the separate contribution of thresholds and adaptation in each of the two pathways to determine which components produce changes in temporal differentiation. Additional studies of sensitizing retinal ganglion cells indicate that adapting inhibitory and excitatory pathways can reproduce the membrane potential fluctuations of sensitizing ganglion cells. We find that simple building blocks in multiple adapting pathways can combine to produce more complex and stronger adaptation.

**MATERIALS AND METHODS**

**Electrophysiology.** For intracellular recording, the intact salamander retina of either sex was held in place under a transparent dialysis membrane containing several 150 – 300 µm holes. Intracellular electrodes were filled with 2 M potassium acetate (200 – 300 MΩ) and guided into the retina under infrared illumination viewed through a CCD camera. On-Off amacrine and ganglion cells were identified by their flash response, receptive field size, and level in the retina. Intracellular recordings were made from eight On-Off cells including four ganglion cells and four amacrine cells. Results are similar for the two cell types, and are pooled in all analyses. Recordings ranged from 10 - 90 minutes in duration.

**Visual Stimulation.** A spatially uniform visual stimulus was projected from a video monitor onto the retina. The stimulus intensity changed every 30 ms, and was drawn from a Gaussian probability distribution with mean intensity, $M$ ($\sim 8 \text{ mW/m}^2$) and standard deviation $W$ (Smirnakis et al., 1997). Contrast was defined as $W/M$, and changed randomly every 20 s to a value between 0.05 and 0.33, drawn from a uniform
distribution. The stimulus lasted 300 s (15 contrast levels) and the identical stimulus sequence was repeated at least two times.

Standard linear model. A linear temporal filter was computed that most closely approximates the entire response of a cell or pathway. This filter $F_L(t)$ is different than the component linear filter of the LNK model, $F_{LNK}(t)$. Linear temporal filters were computed as described (Baccus and Meister, 2002). The stimulus intensity $s(t)$ was normalized to have zero mean, and a standard deviation equal to the contrast. The filter, $F_L(t)$, was computed as the correlation between $s(t)$ and the response $r(t)$ normalized by the autocorrelation of the stimulus. The filter was computed as,

$$F_{LN}(\omega) = \frac{\langle \tilde{s}^*(\omega)\tilde{r}(\omega) \rangle}{\langle \tilde{s}^*(\omega)\tilde{s}(\omega) \rangle}$$

(29)

where $\tilde{s}(\omega)$ is the Fourier transform of $s(t)$, $\tilde{s}^*(\omega)$ its complex conjugate, and $\langle \ldots \rangle$ denotes averaging over 1 s segments spaced every 0.1 s throughout the recording. The denominator corrects for deviations of the video monitor from a white noise distribution (Hunter and Korenberg, 1986). This calculation was performed separately at low (5%) or high (33%) contrast. The filter was normalized in amplitude so that when the filter was convolved with the stimulus to yield a linear prediction $g(t)$,

$$g(t) = \int F_{LN}(t-\tau)s(\tau)d\tau,$$

(30)

the variance of $g(t)$ and $s(t)$ were equal,

$$\int s^2(\tau)d\tau = \int g^2(\tau)d\tau.$$

(31)
**Linear Nonlinear Kinetic model.**

LNK models were optimized as described (Ozuysal & Baccus, submitted). For On-Off cells the model had two pathways. Each pathway consisted of a linear temporal filter $F_{LNK}(t)$, a static nonlinearity, $N(g)$ and a first order kinetic system defined by a transition matrix $Q(u)$. The components were parameterized as described below, and all parameters were fitted together using a constrained optimization algorithm. For each pathway, the stimulus, $s(t)$, was passed through a linear temporal filter, $F_{LNK}(t)$ and a static nonlinearity, $N(g)$,

$$u(t) = N\left(\int F_{LNK}(t - \tau)s(\tau)d\tau\right). \quad (32)$$

Although these two initial stages have the same structure linear-nonlinear (LN) model, the filter and nonlinearity are different functions than those computed for an LN model, and are optimized, rather than computed using reverse correlation. The kinetics block of the model is a Markov process defined by

$$\frac{dP(t)}{dt} = P(t)Q(u), \quad (33)$$

where $P(t)$ is a column vector of $m$ fractional state occupancies such that $\sum_i P_i = 1$, and $Q$ is an $m \times m$ transition matrix containing the rate constants $Q_{ij}$ that control the transitions between states $i$ and $j$, with $Q_{ii} = -\sum_{i \neq j} Q_{ij}$. After this differential equation was solved numerically, the output of the model, $r'(t)$ was equal to one of the state occupancies scaled to a response in millivolts,

$$r'(t) = P_z(t)c + d, \quad (34)$$
where \( c \) and \( d \) are a scaling and offset term for the entire recording.

States and rate constants are diagrammed in Fig. 2A and defined as,

\[
\begin{align*}
P_1 &= R \quad \text{Resting} & R \rightarrow A: & Q_{12} = u(t)k_a & \text{Activation} \\
P_2 &= A \quad \text{Active} & A \rightarrow I_1: & Q_{23} = k_f_i & \text{Fast inactivation} \\
P_3 &= I_1 \quad \text{Inactivated} & I_1 \rightarrow R: & Q_{31} = k_f_r & \text{Fast recovery} \\
P_4 &= I_2 \quad \text{Inactivated} & I_1 \rightarrow I_2: & Q_{34} = k_s_i & \text{Slow inactivation} \\
& & I_2 \rightarrow I_1: & Q_{43} = u(t)k_s_r & \text{Slow recovery}
\end{align*}
\]

(35)

The change in state occupancy was thus determined as

\[
\frac{d\mathbf{P}(t)}{dt} = \mathbf{P}(t)
\]

\[
\begin{pmatrix}
\hat{P}_1(t) \\
\hat{P}_2(t) \\
\hat{P}_3(t) \\
\hat{P}_4(t)
\end{pmatrix}
= \begin{pmatrix}
-u(t)k_a & u(t)k_a & 0 & 0 \\
0 & -k_f_i & k_f_i & 0 \\
k_f_r & 0 & -(k_f_r + k_s_i) & k_s_i \\
0 & 0 & u(t)k_s_r & -u(t)k_s_r
\end{pmatrix}
\]

. (36)

The output of the two LNK pathways were then scaled with independent weights \( w_{ON} \) and \( w_{OFF} \) and summed to give the final output of the model.

Model parameterization. To parameterize the model for fitting, for each pathway, the filter \( F_{LNK} \) was defined as a sum of orthonormal basis functions

\[
F_{LNK}(t) = \sum_{j=1}^{15} \alpha_j f_j(t + \delta),
\]

(37)

where \( \alpha_j \) are the weighting coefficients and \( \delta \) is a single delay parameter for each cell that ranged between 0 and 2 ms. The basis functions were decaying sinusoids of increasing frequency
**Figure 9. Adaptation of temporal differentiation requires the On pathway.**

A. Top. Contrast of a randomly flickering stimulus drawn from a Gaussian intensity distribution with a constant mean. Contrast values ranging from 3 – 33 % were presented to the retina for periods of 20 s. Middle. Sample membrane potential recording lasting 100 s of a ganglion cell responding to the 5 different contrast levels shown. Spikes were digitally removed. Bottom. Expanded segment showing transition between higher and lower contrast. B. Linear filters $F_L$ fit during low and high contrast to membrane potential recordings in control solution (top) and with 30 μM APB (bottom).
\( f_j(t) = \begin{cases} \sin \left( \pi j \left( \frac{2t}{\tau} - \left( \frac{t}{\tau} \right)^2 \right) \right) & 0 \leq t \leq \tau \\ 0 & t > \tau \end{cases} \), \quad (38) 

with \( \tau \) equal to 1 s and were orthogonalized according to (Keat et al., 2001).

The nonlinearity was a sigmoid function parameterized as:

\[
N(x) = a^{\text{erf}(\kappa x + b_1) + 1}k_a^{-1} + b_2 
\]

where \( \text{erf}(x) \) is the error function defined for cumulative Gaussian distributions, \( a, b_1 \) and \( b_2 \) are parameters of the model, and \( \kappa \) was a constant equivalent to the overall variance of the filtered stimulus \( g(t) \). The exponent of \( a \) varies between zero and twenty, and the activation rate constant \( k_a \) in the denominator scales the nonlinearity so that its maximum is one. Thus, the output of the nonlinearity, \( u(t) \), scales the activation rate in the kinetics block between zero and \( k_a \). To optimize the two pathways, all parameters were allowed to vary independently. The only constraints used were boundary constraints for the parameters, which were for the rate constants to be positive, and the slow recovery rate constant \( k_r \) to be slower than 1 s.

**RESULTS**

A randomly flickering visual stimulus was presented to the isolated salamander retina. The stimulus was spatially uniform with an intensity that changed every 30 ms, and was drawn from a Gaussian distribution with a constant mean. Every 20 s, the temporal contrast also changed by varying the standard deviation of the distribution. We
recorded the intracellular membrane potential response from On-Off amacrine and ganglion cells (Figure 9A). Recordings had resting membrane potentials more hyperpolarized than $-65$ mV, lasted at least 300s and contained 15 contrasts. Spikes were digitally removed for analysis of the subthreshold membrane potential.

To quantify the change in temporal processing produced by contrast adaptation, we compared low and high contrast by computing a linear temporal filter, describing the average temporal feature encoded by the cell. At low contrast, the filter was more monophasic, such that the area under the second peak comprised $0.35 \pm 0.05$ ($n = 4$) of the total area under the curve (Fig. 9B). In accordance with previous results (Baccus and Meister, 2002; Beaudoin et al., 2007; Shapley and Victor, 1978), as the contrast increased, the time to the first peak decreased by $16 \pm 2$ ms, and the filter became more biphasic such that the second peak comprised $0.58 \pm 0.16$ of the area.

We blocked transmission through the On pathway using L-A4 (APB), a metabotropic glutamate receptor agonist that blocks synaptic input to On bipolar cells. We found that the change in the time to peak of the filter was similar ($13 \pm 1$ ms) in the absence of the On pathway. However, we found that the change from more integrating during low contrast to more differentiating during high contrast was greatly reduced, with the second peak only having $0.17 \pm 0.08$ ($n = 4$) of the total area at low contrast, and $0.33 \pm 0.12$ at high contrast (Figure. 9B). Thus the full adaptive change in temporal differentiation requires the On pathway.

**LNK model captures the separate contribution of On and Off pathways**

We previously used a linear-nonlinear-kinetic (LNK) model with two parallel pathways to model responses of On-Off cells to changing contrast at a fixed mean nearly to within
Figure 10. Two pathway LNK model captures the contributions of the On and Off pathways.

A. Linear – nonlinear – kinetic (LNK) model of an On-Off ganglion cell. Each of two pathways (Top, On pathway; Bottom, Off pathway), consists of a linear filter, a nonlinearity and a kinetics block. B. Top. Subthreshold membrane potential recordings from an On-Off amacrine cell under control conditions compared to the total output of the two-pathway LNK model. Middle. The On pathway output in the LNK model. Bottom. Membrane potential recordings with APB solution compared with the Off pathway output in the control LNK model.
the accuracy allowed by the variability of the cell (Fig. 10A) (Ozuysal & Baccus, submitted). In each of the pathways of this model, the first stage consists of a linear temporal filter $F_{LNK}$, which represents the average response at this intermediate stage to a brief flash of light. The On pathway contained a filter having a positive first peak (Fig. 10A, top), and the Off pathway contained a filter with a negative first peak. In the next stage, a static nonlinearity $N_{LNK}$ applies a threshold and saturation to the response, as well as setting a baseline sensitivity. The first two stages together have the same structure as a linear-nonlinear (LN) model (Chichilnisky, 2001), commonly used to describe the temporal processing and sensitivity of sensory systems, and as a measure of adaptation. However, the linear filter and nonlinearity of the LN model fit to the entire response have different parameters than those in the LNK model. The final stage consists of a 4-state first order kinetics model, a system that transitions between different states governed by a set of rate constants (Colquhoun and Hawkes, 1977; Hodgkin and Huxley, 1952). The output of the nonlinearity scales one or two of the rate constants in the kinetics block. The coupling of an input to the kinetic system is analogous to a reaction rate that depends on the reactant concentration. Each of the four states represents a different state of the system, including a resting state, $R$, an active state, $A$, and two inactive states $I_1$ and $I_2$. The output of the kinetics block is the active state. The rate constants in the four-state model are the rates of activation, $k_a$, fast inactivation, $k_{fi}$, fast recovery, $k_f$, slow inactivation, $k_{si}$, and slow recovery, $k_{sr}$. For models fit to amacrine and ganglion cells, these rate constants are similar to previously measured rates of bipolar cell synaptic release (Burrone and Lagnado, 2000; Gomis et al., 1999; Neves and Lagnado, 1999). In
Figure 11. Contrast changes the relative contribution of On and Off pathways.

For an LNK model of an On-Off ganglion cell, the overall linear filter $F_L$ for the Off and On pathways separately (top and middle) and the linear filter $F_L$ from the total model output for low and high contrast inputs. Note the overall filter $F_L$ of a pathway or the entire model is different from the component filter $F_{LNK}$ of the model pathway. At each contrast, the standard deviation of the total model output was first normalized to have a standard deviation of one. The amplitude of the filter for individual pathways reflects its sensitivity.
each pathway, the output of the kinetics block is the active state, and the final output is the sum of the two independent pathways.

To verify the correspondence of the LNK model to the separate properties of the On and Off pathways, we first fit a two-pathway LNK model to membrane potential responses recorded in a control condition (Fig. 10A). The correlation coefficient between the model output and the data was (89 ± 5 % n = 4). We then compared the Off pathway of the control model to a single pathway LNK model fit in the presence of APB (Fig. 10B). The correlation coefficient between the Off pathway output in the control case and the model with APB were 96 ± 1% (n = 4). The On pathway of the model contained fluctuations present that were present in the data in the control case, but not when APB was present. This indicates that the drug APB, which selectively suppresses the On pathway, removed the model On pathway without changing the model Off pathway. Thus, despite the combination of two independently adapting pathways, the two-pathway LNK model accurately represents the separate contributions from those pathways, allowing an analysis of how their components give rise to the overall behavior of the cell.

Adaptive change in stimulus feature through differential processing in two pathways

Using the LNK model, we analyzed how much the two separate pathways contributed to the response. We found the On pathway contributes less to the output at low contrast (5 %), such that the response was dominated by the Off filter, which by itself was more monophasic than the filter of the total response (Figure 11). At the highest contrast (33 %), the contribution of the On pathway was similar in magnitude to that of
Figure 12. Differential processing at two stages in the On and Off pathways.

A. Standard deviation for the On and Off pathway outputs for eight amacrine and ganglion cells as a function of contrast after normalizing the the standard deviation of the entire output to one. B. Standard deviation (circles) and mean (squares) of the nonlinearity output $u(t)$ in each pathway as a function of contrast. C. Standard deviation of the kinetics block output $A(t)$ in each pathway as a function of the mean input to the kinetics block $\langle u \rangle$. A standard nonlinearity $N_0$ with a threshold at zero was used to generate $u(t)$ as a function of contrast.
the Off pathway. At low contrast, the On pathway contributed 22 ± 3 % of the total standard deviation of the recording, whereas the Off pathway contributed 78 ± 12 % (n = 8). At high contrast, the relative contribution of the On pathway increased such that the contribution from the two pathways was much more similar (42 ± 2 % for On and 58 ± 2 % for Off). Thus, as the contrast increased, different responses in the two pathways yielded a different mixture of the On and Off pathways, creating a more biphasic response than would result from a single pathway.

Between the extremes of low and high contrast, we then examined in greater detail how the magnitude of each pathway changed as a function of contrast. As the contrast increased, first the output amplitude of the Off pathway increased more rapidly than that of the On pathway (Figure 12A). Then the amplitude of the Off pathway reached a plateau, caused by adaptation in the Off pathway. In comparison, the output of the On pathway steadily increased throughout the contrasts tested.

**Different thresholds have a greater effect on differential processing than different adaptive kinetics**

We then analyzed how each stage of the model in the two pathways contributed to the differential change in output magnitude, and thus the adaptive change in temporal differentiation. Because the linear filters in the two pathways are normalized in amplitude, and the mean of the input is constant, the output amplitude of the first stage in each pathway simply reflects the contrast. Thus no differential processing occurs at this stage except for the difference in the preferred stimulus feature.

We measured how the output magnitude of the nonlinearity varied as a function of its input in the two pathways. Comparing the two nonlinearities, the On pathway had a
higher threshold and more shallow slope than the Off pathway (Figure 10). Due to its lower threshold, the output of the Off nonlinearity increased at a lower contrast than in the On pathway (Figure 12A). However, as contrast increased, because of the steeper slope in the Off nonlinearity, the Off output then began to rise at a slower rate than the On pathway. In comparison, the output of the On pathway rose steadily with contrast above threshold.

To compare the independent contribution of the kinetics block in each pathway, we presented a standardized input \( u(t) \) to the two kinetics blocks, and measured in each pathway the magnitude of the output \( A(t) \), the active state. Previously it was shown that because of the threshold nonlinearity, an increase in contrast causes an increase in both the mean and standard deviation of \( u(t) \). However, only the mean \( \langle u \rangle \) controls adaptation in the kinetics block, thereby controlling the standard deviation of the output \( A(t) \) (Ozuysal & Baccus, submitted). Thus we computed the amplitude of the kinetics block output as a function of the mean input \( \langle u \rangle \). To generate \( u(t) \), we used a nonlinearity \( N_0 \) with a threshold at zero for both kinetics blocks. This caused both the mean and standard deviation of \( u(t) \) to increase linearly with contrast. When \( \langle u \rangle \) increased, the standard deviation of the kinetics block output \( A(t) \) increased quickly at first, but then rose with a decreasing rate as the kinetics block adapted (Figure 12C).

Comparing the two pathways, the standard deviation of the kinetics block as a function of the mean input \( \langle u \rangle \) was similar. The Off pathway, however, adapted slightly more than the On pathway in that on average the standard deviation of the On pathway rose 1.22 ± 0.04 (n = 8) times more than the Off pathway across different mean inputs. Thus,
Figure 13. Dependence of pathway output on specific nonlinearities and adaptive kinetics.

A. Output vs contrast for the On (top) and Off (bottom) pathways of an On-Off amacrine cell, compared with the same curves after exchanging the nonlinearities or the kinetics blocks of the two pathways. Diagonal line labeled $\alpha_N$ indicates the average slope of the output vs contrast curve when the nonlinearities were exchanged. Point labeled $\beta_N$ indicates the rate constant of adaptation when the nonlinearities were exchanged, computed from an exponential fit to the curve. B. The values for $\alpha$ (left) and $\beta$ (right) after exchanging kinetics blocks ($\alpha_K$, $\beta_K$, top) and nonlinearities ($\alpha_N$, $\beta_N$, bottom) are plotted against the values of $\alpha_C$ and $\beta_C$ in the control condition. The scale is logarithmic.
differences in the output of the two pathways with contrast appeared to be caused more by the different nonlinearities than by the different kinetics blocks.

To test this idea further, we used the two-pathway model and exchanged either the nonlinearities or kinetics blocks and measured the resulting effects on each pathway. First we switched the kinetics blocks while keeping the filters and nonlinearities fixed. We found a small but significant change in the output of the two pathways as a function of contrast (Fig. 13A). Then we exchanged the nonlinearities and saw a much larger effect, that the change in output magnitude of the On pathway was much more similar the Off pathway in the control condition, and vice-versa.

We further quantified these effects by computing two parameters of the relationship between the contrast, $c$ and output magnitude $\sigma$ for each pathway. We computed the average slope $\alpha$ of $\sigma(c)$, reflecting the average increase in output magnitude with contrast. A more shallow slope indicated more adaptation (Figure 13A). Then we fit an exponential function to $\sigma(c)$, measuring the decay constant $\beta$ for how fast $\sigma(c)$ began to plateau with contrast. This indicates how rapidly adaptation occurred as contrast increased, with a smaller value indicating that adaptation developed at a lower contrast. Figure 13B shows the values for the change in output $\alpha$ and rate of adaptation $\beta$ for the two pathways in the control condition ($\alpha_C$, $\beta_C$), when when the kinetics blocks were exchanged ($\alpha_K$, $\beta_K$) and when the nonlinearities were exchanged ($\alpha_N$, $\beta_N$). In the control condition, the two pathways differed in the change in output $\alpha_c$ by a factor of $3.2 \pm 0.2$, with the On pathway having a greater slope reflecting less adaptation. Exchanging the kinetics caused the slope $\alpha_k$ to be only a factor of $1.3 \pm 0.06$ different than $\alpha_c$, a change of 30%. This factor was computed by averaging $\alpha_{c(ON)}/\alpha_{N(ON)}$ and
\( \frac{\alpha_{K(\text{OFF})}}{\alpha_{C(\text{OFF})}} \). In comparison, changing the nonlinearities caused the slope \( \alpha_N \) to be a factor 2.94 ± 0.34 different from \( \alpha_C \) in the control case, a change of 194%. Thus the change produced by exchanging the nonlinearities was 6.5 times that produced by exchanging the kinetics blocks. We then compared the control rate of adaptation \( \beta_C \) for the two pathways, which differed by a factor of 5.7 ± 0.9. Exchanging the kinetics blocks caused the rate \( \beta_K \) to be only a factor of 1.26 ± 0.07 different than \( \beta_C \), whereas exchanging the nonlinearity caused \( \beta_N \) to be a factor of 4.26 ± 0.72 different than \( \beta_C \).

Thus, exchanging the nonlinearities caused a change in the adaptive rate 12.5 times greater than exchanging the kinetics. Thus, the amount of adaptive change in temporal differentiation is controlled primarily by the different nonlinearities in the two pathways, with a smaller contribution from the different adaptive kinetics. In comparison, the contrast at which the adaptive change in the temporal filter occurs is controlled almost exclusively by the differences in the two nonlinearities.

This does not suggest that the kinetics block plays a small role in other adaptive properties. Across contrasts, the action of the kinetics block contributes to changing the speed of the temporal filter and the gain (Ozuysal & Baccus, submitted). These effects, however are distinct from the change in temporal differentiation controlled by differential output in the two pathways.

**Using multiple pathways to model sensitization**

We tested whether multiple LNK pathways could be used to model the effects of an inhibitory pathway in the retina. Although inhibitory connections are not necessary to produce standard forms of contrast adaptation, it is thought that several types of amacrine cells might modulated contrast adapting circuitry to create more complex effects upon a
Figure 14. Two pathway LNK model captures sensitization.

A. Linear – nonlinear – kinetic (LNK) model of a sensitizing ganglion cell. Each of two pathways (Top, Excitatory pathway; Bottom, inhibitory pathway), consists of a linear filter, a nonlinearity and a kinetics block. The output of the inhibitory pathway was subtracted from the first pathway just prior to the threshold nonlinearity. B. The membrane potential response of a sensitizing ganglion cell compared to the LNK model output for a transition to low contrast (left). At right is shown the response at a compressed timescale.
contrast switch. One example of such a modulation is sensitization in retinal ganglion cells (Kastner & Baccus, 2011). Sensitizing retinal ganglion cells elevate their sensitivity and activity following a high contrast stimulus.

This elevated sensitivity compensates for a loss of sensitivity in a separate adapting population at the transition to low contrast. Together, the two populations maintain responsiveness to a changing stimulus environment when each individual population would fail to encode the stimulus.

We recorded from sensitizing ganglion cells, and found that at the transition to low contrast, the membrane potential depolarized 100 – 300 ms after the transition. This depolarization than decayed in 1 – 3 seconds to a more hyperpolarized baseline (Fig. 14B). In addition, the cell adapted to both contrasts, such that fluctuations at low contrast were larger than expected from a cell that did not adapt. To model sensitization, we used a two-pathway LNK model with adapting inhibitory and excitatory pathways (Fig. 14A). Instead of summing the two pathway outputs as in the case of On-Off ganglion cells, the inhibitory pathway was summed with the excitatory pathway just before the threshold in the excitatory pathway. This combination is consistent with a previous simplified model of sensitization (Kastner & Baccus, 2011) and corresponds to presynaptic inhibition of an amacrine cell on the ganglion cell. This produces an output that is processed by two adaptive modules. We found that this model captured the membrane potential of a sensitizing ganglion cell, capturing both fluctuations at high and low contrast, and the depolarization at the transition to low contrast (Fig. 14B). The correlation coefficient
between the model and average response of the cell was 90%, whereas it was 92 ± 1% between repeats of an identical visual stimulus.

**DISCUSSION**

We have used a linear-nonlinear-kinetic model to analyze how different properties of threshold and adaptive kinetics in parallel pathways interact to perform a computation, namely the adaptive change in temporal differentiation widely seen in different sensory systems. The LNK model breaks down the cell’s response into smaller subsystems, first by separating On and Off pathways, then further compartmentalizing computational function into feature selection, nonlinear distortion and thresholding, and adaptation. The accuracy of this model, its ability to capture adaptive properties and the correspondence of its components to distinct neural pathways (Fig. 10) allow us to localize a potentially complex response into simpler computational elements.

Systems that can be accurately captured with a linear-nonlinear (LN) model do not change their properties of temporal filtering or sensitivity with a change in stimulus statistics. Thus, a change in the parameters of the LN model has served as a definition of adaptation. The LNK model localizes the nonlinear dynamic properties that change gain and temporal filtering into a single adaptive kinetics block. Both On and Off pathways adapt independently, in that the LNK model for each pathway has adaptive kinetics that changes the gain with contrast (Ozuysal & Baccus, submitted). Additionally, the Off pathway produces a greater change in the speed of temporal filtering than the On pathway (Ozuysal & Baccus, submitted). However, although the different adaptive kinetics in the two pathways do make a small contribution to the adaptive change in temporal differentiation, the primary source for this adaptive change is the different thresholds in
the two pathways (Fig. 12 – 13). Thus we find that adaptive temporal differentiation can be produced through the combination of nonadapting pathways.

Changes in temporal differentiation can be generated using different computational components. Photoreceptors have a more biphasic response at higher luminance (Baylor and Hodgkin, 1974), yet use only a single biochemical pathway to convey the light response (Pugh et al., 1999). Theoretical analysis of the LNK model indicates that a single neural pathway could, in fact, generate changes in temporal differentiation given appropriate rate constants (Ozuysal & Baccus, submitted). However we find that given the specific adaptive properties of the On and Off pathways of On-Off cells, both pathways are needed to generate changes in temporal differentiation. This illustrates that analysis of individual cells using a specific, accurate model is essential to understanding how different cells produce adaptive computations.

Previous experiments give evidence as to the correspondence of different stages of the LNK model with different levels in the circuit. Because bipolar cells do not show strong rectification but ganglion cells do, the threshold likely arises at the bipolar cell synaptic terminal. One possible source of the different thresholds in the two pathways is differential expression of voltage-dependent calcium channels in different types of bipolar cells (Pan, 2000). An alternative source is differential inhibition onto bipolar cell terminals (Pan, 2001), which would set the resting potential at different levels relative to the activation threshold of calcium channels in the synaptic terminal.

**Two pathways implement a change in the rules of efficient coding**

The correspondence of the LNK model with both adaptive function and cellular properties allows us to observe how the two are connected. The rules of efficient coding
are known to change when the signal strength changes. Due to the dominance of low temporal frequencies in natural visual scenes, it can be an efficient strategy to remove these slow correlations, thus giving more equal weight to high and low frequency signals (Atick, 1992; Van Hateren, 1993). To reduce low frequency input, sensory neurons encode with a biphasic filter, computing the difference between the light intensity and a reference level measured at a previous interval of time. This approach however can come at a cost when signals are weak and noisy – rather than computing the difference between noisy signals, the more efficient strategy is not to decorrelate, but to simply exclude high frequency signals.

Here we find that temporal differentiation increases when the contrast is high enough to exceed the higher threshold of the On pathway. Thus, by producing the opposing phase of the filter, the On pathway conveys the reference level only when the contrast is sufficiently high. By analyzing the nonlinear and adaptive components of the neural code, we find that different rules of efficient coding are selected by different thresholds in two neural pathways.
CHAPTER 4 - GENERAL DISCUSSION

Contrast adaptation in the retina comprises many different changes that occur at different time scales. This adaptive changes have great similarity across different sensory systems and species. Yet, there is also substantial diversity among different cell types. The accuracy of the LNK model in capturing all these properties shows that an apparently complex phenomenon may in fact be the result of simple building blocks interacting with each other. One important feature of the LNK model is that it achieves these adaptive properties intrinsically, not needing a separate pathway that computes the contrast information. So essentially while the model adjusts its dynamical range to respond to changes in the surrounding environment, information continues to flow through the same channel, starting from the first block with the preferred feature selected by the linear filter. This also means that when we expand the LNK model by including new modules that adapt to other statistics or new pathways that combine multiple stimulus features, the kinetics block will still function to control adaptation of the final combined response. Although the analysis of such a complex network of connections will be computationally more challenging, the simplicity of the building blocks will help in deriving intuition about how these components connect in different ways to produce complex adaptive behavior in the retina and in the nervous system in general.

Relationship with mean adaptation

Although the initial goal of this work was to study and understand contrast adaptation in detail, the biophysical nature of the model has made it possible to propose several important mechanisms about luminance adaptation in the retina as well.
Extending the model to one that adapt to both the mean luminance and contrast would involve the addition of an initial stage that adapts to the mean luminance. This initial module to adapt to the mean stimulus could be a simplified version of a model proposed previously for the phototransduction cascade (Van Hateren, 2007), or it could be as simple as a monophasic linear filter followed by an adapting kinetics block. In this case, because the mean input to the kinetics block would change when the mean stimulus changed, no nonlinearity would be needed. This arrangement would be an LKLNK cascade, with the final LNK pathway corresponding to our current model of contrast adaptation. Because the second linear filter is strongly biphasic, and does not transmit information about the mean, this arrangement would likely make mean and contrast adaptation independent, as has been previously observed for mid to high level intensities (Mante et al., 2005).

The adaptive kinetics block in the model adapts to its mean input. Because we have fixed the mean of the initial stimulus in these experiments, this mean signal level at the input of the kinetics block derives not from the mean stimulus, but from a rectified version of the stimulus. However, if the mean value of the stimulus is transmitted to the final kinetics block and not filtered out in the previous stage, than the final kinetics block will also adapt to the mean stimulus. At lower mean luminance, linear filters in the retina become more monophasic, and thus transmit more information about the mean stimulus. Thus, as the mean light intensity decreases, the second linear filter would start to transmit more information about the mean stimulus, and the final adaptive stage would start responding to both mean and contrast changes in the input stimuli. This switching of adaptive sites at different mean luminance levels has been experimentally observed
(Dunn et al., 2007). This is just another example of how experimentally observed phenomena that are seemingly complex can be explained as a byproduct of the interaction between two simple separate modules in the retinal circuitry.

**Addition of a spiking block**

In all the studied examples, membrane potentials recordings where spikes were digitally removed were used, Thus the LNK model parameters and the conclusions drawn about contrast adaptation pertain to sites of adaptation before spike generation occurs. Expanding the current model to replicate spike recordings is a natural extension in reaching to a unified understanding of contrast adaptation in the retina. Although the modeling aspects and the integration of a new spiking module to the current framework is a problem that requires nontrivial research and design efforts, the fact that integrate and fire models have already been used in models that replicate contrast adaptation (Gaudry and Reinagel, 2007), and also previous studies describing mechanisms like inactivation of slow Na channels as candidates for giving rise gain control during spike generation (Kim and Rieke, 2003), indicates that a considerable amount of progress has already been made in this direction.

Adding a spiking block to this LNK pathway would not only give us a model that captures all stages of contrast adaptation, but also it will make it possible to study the relationship between the two adaptive blocks and how they interact. In the first example of the Chapter 3, we have seen how using simple biophysical blocks can help in analyzing the interaction between adjacent modules. A similar approach can be used to study how the subthreshold adaptive mechanisms combine with an adaptive spiking mechanism.
Another benefit of augmenting the model in this direction is that the output of the whole model becomes the spike rate, which makes it possible to use this approach in many more studies; since extracellular multi-electrode array recordings is being widely used to gather spiking recording from many ganglion cells simultaneously.

**Combining multiple pathways for making the apparently complex simple**

Consideration of both mean adaptation and spiking involves the use of a single pathway. However the adaptive phenomena in the retina and in the nervous system in general cannot be limited to the use of a single feed forward pathway. As the adaptation, the cell type, or the stimuli become more complex multiple pathways are needed. One of the strongest advantages of using simple biophysically inspired building blocks is that once the connections are defined, it is fairly straightforward to construct a multiple pathway model and use the same analysis tools to understand how these pathways interact.

Other than analyzing adaptation in cells such as On-Off cells, or adding inhibitory effects to modulate contrast adaptation as in the sensitization model, multiple pathways can also be used for understanding how adaptation occurs for a spatially complex stimulus. The use of full field stimuli, although it makes the analysis simpler, limits the scope of adaptation changes to temporal changes. It is expected that using multiple pathways, the framework we have described can be expanded to spatial adaptation such as motion adaptation (Olveczky et al, 2007) pattern adaptation (Hosoya et al., 2005), and adaptation to other multidimensional sensory input in the nervous system.
APPENDIX

Supplemental Figure S1. LNK model of an ON-OFF Ganglion cell.

Comparison of LNK model and membrane potential of an On-Off ganglion cell for 200 s of a continuous recording. Each line is a 20 s segment at a single contrast. Left to right, contrast value, example segment of stimulus intensity during that segment and the membrane potential recording compared to LNK model. Action potentials were digitally removed from the recording.
Supplemental Figure S2. Discarded topologies for the kinetics block.

Four-state kinetics block topologies that were discarded because of either lack of slow adaptation or because fast and slow dynamics were coupled, unlike the experimental recording. A. Top. Line topology, in which the return pathway from inactivated to resting states is through the active state. Middle. Comparison of a recording with the LNK model shown in the main text. Bottom. Comparison of the same recording with the LNK line-topology model. B. Top. Loop topology, in which recovery from the activated state traverses a path with slow rate constants. Middle. Comparison of a recording with the LNK model shown in the main text. Bottom. Comparison of the same recording with the LNK loop-topology model.
Supplemental Figure S3. Bipolar cell specific dynamics and error of kinetic parameters.

A. Top. Stimulus intensity at a fixed contrast of 24 %. Middle. For a bipolar cell, the instantaneous gain as represented by the resting state $R(t)$ of the kinetics block. Bottom. Comparison of the LNK model and membrane potential response.

B. The error between the LNK model and the recording was computed when single parameters were varied from their optimal value, indicated by zero. The error is the normalized error measure used to fit the model (see Supplemental Experimental Procedures). For each plot, the error value was computed by varying the parameter alone. In addition, the error was computed by holding the parameter fixed at the indicated value and then reoptimizing the model to allow other parameters to compensate for the perturbation. Shown for a single cell are the base of the nonlinearity exponent, $a$, nonlinearity offset, $b_1$, maximum activation rate, $k_a$, fast inactivation rate, $k_{fi}$ and fast recovery rate, $k_{fr}$. All parameters are normalized by optimal value of the parameter, and are shown as a fractional change, except for $b_1$, which was normalized by the full range the nonlinearity input $g(t)$ spanned by the stimulus. Over 12 cells, to deviate from the optimal error by 2%, the fractional change needed was $0.12 \pm 0.02$ for $a$, the exponent of the nonlinearity, $0.13 \pm 0.01$ for $b_1$, the input offset of the nonlinearity, where normalization is by the full range of the nonlinearity input, $0.27 \pm 0.04$ for $k_a$, the activation rate, $0.23 \pm 0.04$ for $k_{fi}$, the fast inactivation rate and $0.24 \pm 0.05$ for $k_{fr}$, the fast recovery rate.
A

Intensity

Gain

Data
Model

10 mV
100 ms

B

Single parameter varied alone
Parameter varied with re-optimization

-0.5 0 0.5
\(\Delta a\)

-0.1 0 0.1
\(\Delta b\)

-0.3 0 0.3
\(\Delta k_{a}\)

-0.5 0 0.5
\(\Delta k_{fi}\)

0 2
\(\Delta k_{fr}\)

2% error
Supplemental Figure S4. Linear-nonlinear model fails to capture ongoing adaptation and asymmetric fast responses.

Top. Stimulus intensity at a fixed contrast of 35%. Comparison of LN model and LNK model output with the membrane potential recording from an Off-type amacrine cell.
Supplemental Figure S5. Theoretical estimates for adaptive changes.

A. For the kinetics block in Figure 8A, the derived ratio of gain between low and high contrast as a function of two parameters, fast inactivation, $k_{fi}$ and fast recovery, $k_{fr}$.

Gain was computed directly from rate constants using eq. 3. Both parameters are shown
normalized by the mean activation rate, $k_a$. B. Theoretical change in kinetics as a function of fast inactivation, $k_f$, normalized by the mean activation rate, $k_a$. Also shown is the simulation from Figure 8D as a function of $k_f$. The theoretical change was computed using eqs. 25 and 27. The slight discrepancy is because the fourth state used in the simulation was not accounted for in the theoretical calculation. C. The impulse response functions, $F_k$, for resting, active and inactive ($I_1$) states were measured by presenting impulses $\Delta u$ added to a baseline input $u(t)$, representing the average value at low or high contrast. Left. Rate constants were chosen to show a small change in kinetics and temporal differentiation, and show small changes in the level of inactivation as a function of the contrast. Right. Rate constants were chosen to show a larger change in kinetics and temporal differentiation, and show a larger change in the level of inactivation. Dotted lines indicate the trough of the undershoot of the impulse response in the active state. For high contrast, $\Delta I_{1H}$ indicates the amount of inactivation at the time of the trough, and $\Delta R_{1H}$ indicates the smaller recovered occupancy in the resting state at the time of the trough. Because for a three state model, $\Delta A = -(\Delta I_1 + \Delta R)$, when inactivation $\Delta I_{1H}$ is greater than $-\Delta R$, an undershoot in the active state occurs. For low contrast, $\Delta I_{1L}$ and $\Delta R_L$ indicate corresponding values at the time of the low contrast trough. In this case the change in inactivation is similar to the change in the resting state, and little undershoot occurs in the active state.
REFERENCES


