NEUROSCIENCE

# Short-term plasticity and context-dependent circuit function: Insights from retinal circuitry

**Zixuan Deng[1], Swen Oosterboer[1], Wei Wei[2]***

**Changes in synaptic strength across timescales are integral to algorithmic operations of neural circuits. However, pinpointing synaptic loci that undergo plasticity in intact brain circuits and delineating contributions of synaptic plasticity to circuit function remain challenging. The whole-mount retina preparation provides an accessible platform for measuring plasticity at specific synapses while monitoring circuit-level behaviors during visual processing ex vivo. In this review, we discuss insights gained from retina studies into the versatile roles of short-term synaptic plasticity in context-dependent circuit functions. Plasticity at single synapse level greatly expands the algorithms of common microcircuit motifs and contributes to diverse circuit-level behaviors such as gain modulation, selective gating, and stimulus-dependent excitatory/inhibitory balance. Examples in retinal circuitry offer unequivocal support that synaptic plasticity increases the computational capacity of hardwired neural circuitry.**



## INTRODUCTION

Synaptic strength varies across timescales based on the history of its activity. As a fundamental property of neuronal signaling, synaptic plasticity is an intrinsic component of the computational algorithm of a neural circuit. However, integrating plasticity rules into circuit analysis remains a challenge for intact brain circuits, primarily because synaptic plasticity induced by physiological network dynamics is difficult to track and manipulate in vivo. In the isolated whole-mount retina preparation, local circuitry is preserved, and synaptic plasticity can be monitored by patch clamp recordings, while the retina carries out its physiological function of visual processing. These advantages make the retina an excellent model system for incorporating synaptic plasticity into the fundamental logic of neural computation.

The vertebrate retina is highly organized in layers and columns and contains both specialized and generic circuit elements (*1*, *2*). Five broad retinal cell classes are organized into three cellular layers and two intervening synaptic layers (Fig. 1A). At the first step of visual processing, rod and cone photoreceptors detect light signals that are topographically mapped to the visual space. A columnar organization across layers implements feedforward signaling from photoreceptors to bipolar cells to retinal ganglion cells (RGCs). This pathway converts images focused on the photoreceptors into the excitatory drive of RGCs. Lateral interactions by local and long-range signaling of horizontal cells and amacrine cells within each synaptic layer modify this feedforward pathway (Fig. 1A). The first synaptic layer, the outer plexiform layer, features adaptive signaling of phototransduction and synaptic release from photoreceptors, as well as lateral inhibition from horizontal cells (Fig. 1B). The second synaptic layer, the inner plexiform layer, showcases remarkable cell type diversity and further elaboration of circuitry. Diverse types of bipolar cells, amacrine cells, and RGCs send their neurites to distinct sublaminae of the inner plexiform layer, resulting in a rich repertoire of synapse types, neuromodulatory mechanisms, and microcircuit motifs (Fig. 1B). Extensive interactions of local and wide-field circuit components enable the retina to extract diverse visual features from visual inputs over space and time, which are then relayed to downstream brain regions via spiking activities of distinct RGC types (*3*).

Signal processing by the retina exhibits hallmarks of neural circuit behavior. One such hallmark is that functional connectivity is context dependent and adaptive to inputs (*4*). Synaptic plasticity is well positioned to contribute to this flexible circuit behavior because it is inherently stimulus dependent. In this review, we focus on short-term plasticity of chemical synapses, i.e., the depression and facilitation of synapses in timescales of milliseconds to seconds and their implications for circuit function. We recognize that many other aspects of plasticity play pivotal roles in retinal function and dysfunction, such as neuromodulation of chemical synapses and the plasticity of electrical synapses. These topics are not included in this article but have been discussed in recent excellent reviews [e.g., neuromodulation in (*5*), homeostatic and developmental plasticity in (*6*), plasticity of electrical synapses in (*7*), and plasticity induced by photoreceptor loss in (*8*)]. In the following sections, we will first summarize short-term plasticity mechanisms in the retina and then discuss examples on how plasticity contributes to stimulus-dependent visual processing by the retinal circuitry.

## SYNAPTIC DEPRESSION

### Ribbon synapses

Retinal ribbon synapses are specialized presynaptic structures of photoreceptors and bipolar cells that bring a large number of synaptic vesicles to the vicinity of the active zone for continuous and graded neurotransmitter release [see reviews in (*9*, *10*)]. The presynaptic release machinery of ribbon synapses uses both conventional and ribbon-specific molecular components, including the t-SNARE syntaxin 3B for multivesicular release (*11*, *12*), calcium sensors synaptotagmins 1 and 7 (*13*), L-type voltage-gated calcium channels with rapid activation and slow inactivation kinetics (*14*–*22*), and additional T-type calcium channels in bipolar cells (*18*–*20*, *23*). The molecular compositions and ultrastructures of ribbon synapses define the timescales and kinetics of their activity-dependent changes in synaptic strength.

Synaptic depression is prevalent at ribbon synapses and is central to adaptive sensory transduction. During repeated or

[1]The Committee on Neurobiology Graduate Program, The University of Chicago, Chicago, IL 60637, USA. [2]Department of Neurobiology and the Neuroscience Institute, The University of Chicago, Chicago, IL 60637, USA.
*Corresponding author. Email: weiw@uchicago.edu

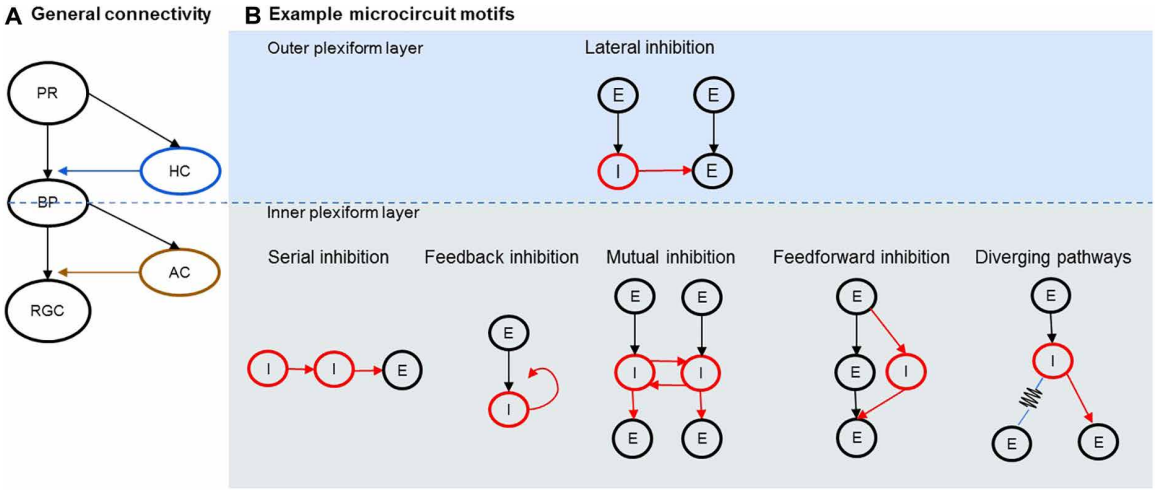


**Fig. 1. Circuit organization of the vertebrate retina.** (**A**) Overall connectivity pattern of five classes of retinal neurons. (**B**) Example canonical microcircuit motifs in the two synaptic layers: outer and inner plexiform layers. PR, photoreceptor; HC, horizontal cell; BP, bipolar cell; AC, amacrine cell; E, excitatory neuron; I, inhibitory neuron.

prolonged activation of photoreceptors and bipolar cells, synaptic depression can be caused by the depletion of readily releasable pool of synaptic vesicles, calcium channel inactivation, or postsynaptic receptor desensitization (*24*–*29*). In addition, synaptic release from photoreceptors is indirectly modulated by the regulation of the phototransduction cascade, which plays an essential role in the adaptation of photoreceptor signaling across a vast range of ambient light levels (*30*, *31*).

### Amacrine cell synapses

Amacrine cells are the most diverse group of retinal neurons and release neurotransmitters γ-aminobutyric acid (GABA) or glycine from nonribbon synapses [reviewed in (*32*)]. Most amacrine cells also release additional neurotransmitters and neuromodulators such as glutamate, acetylcholine, dopamine, and various neuropeptides. Presynaptic release mechanisms of different amacrine cell types show molecular diversity. For example, different cell types express different sets of presynaptic voltage-gated calcium channels [reviewed in (*33*)]. L-type calcium channels are predominant calcium channels in AII amacrine cells (*34*), L- and N-types in A17 amacrine cells (*35*), N- and P/Q-types in starburst amacrine cells (SACs) (*36*–*38*). In addition, calcium from internal stores can also contribute to the release from certain amacrine cell types (*39*–*43*).

Despite the diversity in presynaptic release mechanisms, synaptic depression at subsecond timescale is commonly observed at various amacrine cell types across species [e.g., (*24*, *44*–*46*)]. For example, in the mouse retina, synaptic release from both SACs and AII amacrine cells shows paired pulse depression at subsecond interpulse intervals (*24*, *45*, *46*), although these two cell types use different presynaptic calcium channels. An exhaustive characterization of plasticity across amacrine cell types is yet to be completed.

## SYNAPTIC FACILITATION

Facilitation observed in the retina so far is largely attributed to network mechanisms rather than to presynaptic release machineries. In bipolar cells, facilitated glutamate release can result from reduced presynaptic inhibition from amacrine cells (*47*–*50*) or from the cholinergic feedback excitation from SACs via α7 nicotinic acetylcholine receptors (*51*). In amacrine cells, paired pulse facilitation of amacrine cell outputs has been reported at longer interpulse intervals (~2 s) in goldfish amacrine cells (*52*) and mouse AII amacrine cells (*24*). For goldfish amacrine cells, this facilitation is partially reduced by GABA type A receptor blockade, suggesting that facilitated release may be caused by a combination of network and presynaptic mechanisms (*52*).

In addition to the network effect of disinhibition, several other forms of synaptic potentiation in the retina depend on metabotropic signaling or postsynaptic receptors. For example, metabotropic glutamate receptor 1–dependent potentiation of synaptic release has been reported in goldfish amacrine cells (*53*) and mouse rod bipolar cells (*54*). Pharmacologically elevating cyclical adenosine monophosphate (cAMP) levels in mouse AII amacrine cells leads to potentiated glycine release to Off cone bipolar cells through increasing the readily releasable vesicle pool (*55*). Postsynaptic receptor potentiation has also been reported. At the goldfish ribbon synapse from bipolar cells to amacrine cells, postsynaptic potentiation can be induced within a few minutes and is dependent on calcium-permeable AMPA receptors and intracellular calcium increase (*56*). At the synapse between mouse On bipolar cells and On RGCs, postsynaptic potentiation is mediated by *N*-methyl-D-aspartate receptor–dependent AMPA receptor trafficking similar to the mechanism underlying long-term potentiation in hippocampal CA1 cells (*57*). Functional roles of these plasticity mechanisms during visual processing await future studies.

## LINKING SYNAPTIC PLASTICITY TO CIRCUIT FUNCTION

Synaptic plasticity diversifies signal transformation between pre- and postsynaptic neurons by implementing gain control, temporal filtering, and altering the rules of synaptic integration [e.g., (*58*–*61*)]. To link this synaptic-level effect to circuit function, one needs to pinpoint the synaptic loci in the circuit that undergo plasticity in response to physiological stimuli. The consequence of changing synaptic strength then needs to be tracked along downstream neurons in the network to the circuit output. Tackling these questions in the

retina has been facilitated by its clearly defined inputs and outputs, as well as extensive functional and connectomic characterization of connectivity. In the following paragraphs, we will discuss several recent examples on how dynamic changes of synaptic strength contribute to various circuit-level computations. These examples highlight the profound and diverse effects of short-term plasticity on network computations that are tailored to inputs. A more exhaustive discussion of well-known computations in the retina is available in a recent book (*62*).

## Diverse forms of gain modulation

Activity-dependent changes in synaptic strength can directly influence the gain of circuit outputs. Gain control in the retina starts in the phototransduction cascade of photoreceptors, which allows them to signal light fluctuations across a range of mean luminance levels (*63*, *64*). Further implementation of gain modulation occurs at various steps in downstream circuits (*65*), with the bipolar cell output as one of the key sites of gain control. In general, depression of the excitatory synapse from bipolar cells to RGCs contributes to the adaptation of RGC spiking responses (*66*–*68*), while depression at inhibitory synapses from amacrine cells to bipolar cells contributes to the sensitization of RGC responses via disinhibition of bipolar cell excitation (Fig. 2) (*47*–*50*, *69*, *70*). This dichotomy of RGC adaptation and sensitization resulting from depressed feedforward excitation versus depressed feedback presynaptic inhibition appears to be a common theme for multiple species including zebrafish, mice, salamander, and primates (*47*–*50*). Modeling indicates that these opposing forms of gain modulation provide complementary advantages of visual encoding. Adaptation is beneficial for encoding changes of stimulus statistics and prevents saturation, while sensitization promotes accurate encoding of naturalistic scenes and preserves the sensitivity of weak signals (*47*, *49*).

The relationship between synaptic plasticity and circuit-level gain modulation is more nuanced and dynamic in specific RGC circuits. For example, in the converging pathway from cones ➔ cone bipolar cells ➔ midget and parasol ganglion cells in the primate retina, signal-to-noise level is improved along this pathway due to the pooling of multiple presynaptic inputs onto the postsynaptic neuron. The synaptic locus of adaptation shifts along this pathway according to the signal-to-noise level of the visual input. Under dim light, single-photon responses of photoreceptors are noisy, and adaptation occurs in the form of synaptic depression at the downstream cone bipolar cell presynaptic terminal, which pools convergent photoreceptor inputs for an improved signal-to-noise level (*66*). In contrast, under brighter light conditions when cone photoreceptor responses become less noisy, the locus of adaptation switches from cone bipolar cells to cone photoreceptors (*66*).

Subtleties in circuit-level gain control arise from the integration of synaptic plasticity with the unique set of cellular- and network-level properties of each circuit to support its specific visual processing function. For example, both midget ganglion cells in the primate retina and the On-Off direction-selective ganglion cells (DSGCs) in the mouse retina can be sensitized by a period of visual stimulation via amacrine cell–mediated disinhibition of their bipolar cell excitatory inputs (*49*, *50*). However, sensitization of these two cell types differentially depends on the spatial frequency of the stimulus. Midget ganglion cells are sensitized by high contrast or moving stimuli that cover both receptive field center and surround but are not sensitized by stimuli restricted to the receptive field center (*49*). This is likely due to the involvement of GABAergic wide-field amacrine cells that require more extensive visual stimulation (*49*). In contrast, mouse On-Off DSGCs can be sensitized by local stimuli restricted to a subregion of their receptive field center, which is possibly explained by narrow-field glycinergic amacrine cells underlying depressed presynaptic inhibition of mouse bipolar cells instead of the wide-field amacrine cell in the primate midget ganglion cell circuit (*50*). Furthermore, sensitization patterns of mouse On-Off DSGCs are different for On versus Off responses and for cells in dorsal versus ventral retina, which may reflect adaptive specializations of mouse retinal circuitry to different visual scene statistics in the upper and lower visual fields. Besides sensitization, adaptation of different mouse RGC types also occurs at different spatial scales (*71*), and the underlying mechanisms are not yet fully understood.

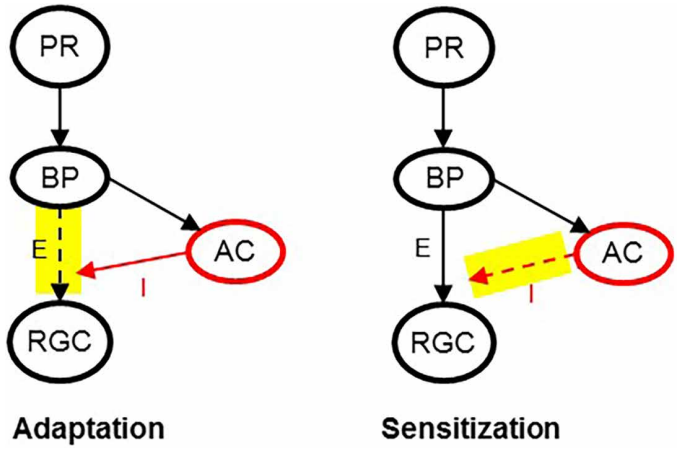


**Fig. 2. Roles of synaptic plasticity in the adaptation and sensitization of RGCs.** Depression of excitatory inputs from bipolar cells contributes to RGC adaptation, while depression of inhibitory inputs from amacrine cells contributes to RGC sensitization. Yellow regions indicate loci of plasticity.

## Encoding different stimulus features

Synaptic plasticity can affect signal processing in ways that extend beyond gain control. Studies in rodents demonstrate that rod bipolar cell ribbon synapses are highly prone to depression. Mouse rod bipolar cell signaling can be depressed by single-photon events, indicating that gain control starts to operate at very low light levels (Fig. 3, darkness) (*72*). At higher ambient light levels, rod bipolar cells exhibit a biphasic depolarizing response to light increase: a transient peak at light onset and a subsequent sustained depolarization with smaller amplitude for the duration of the elevated light level (*73*). This biphasic waveform arises from rapid, partial depletion of vesicle pool upon the light onset and its subsequent replenishment during prolonged illumination (*73*). Biphasic responses of rod bipolar cells convey two features of the visual stimulus: temporal contrast encoded in the transient component and the steady-state ambient luminance encoded in the sustained component (Fig. 3, dim light condition) (*73*). When the ambient light level becomes even brighter, synaptic vesicles of rod bipolar cells are fully depleted, and these cells can no longer detect additional light increase. However, under this condition, when the light intensity decreases for a sufficiently long time, rod bipolar cells can recover at least partially from vesicle depletion and signal a subsequent light

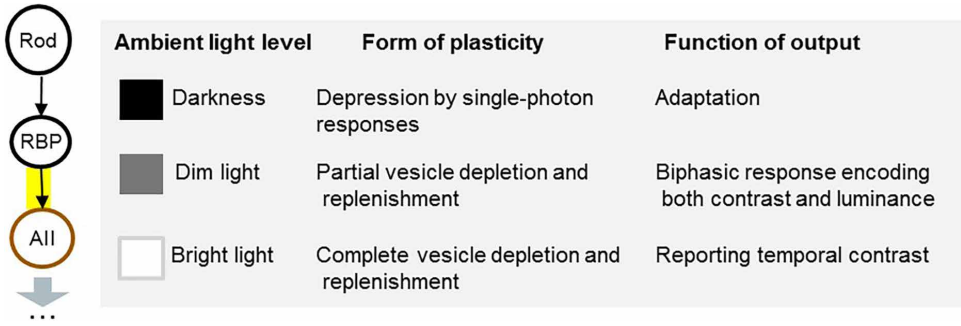


**Fig. 3. Dynamics of synaptic depression and recovery underlie the encoding of different stimulus statistics by rod bipolar cell output.** RBP, rod bipolar cell; AII, AII amacrine cell. Yellow shade indicates the locus of plasticity.

increase, thereby producing a signal modulated by contrast changes between dark and light phases at certain temporal frequencies (Fig. 3, bright light condition) (*67*). Therefore, stimulus-dependent dynamics of vesicle depletion and replenishment can contribute to the encoding of multiple types of visual information under different visual conditions (Fig. 3).

### Alternative algorithm of serial inhibition motif

Interaction of synaptic plasticity and network dynamics can profoundly influence the algorithm of canonical circuit motifs. For example, two serially connected inhibitory neurons upstream of the output neuron are generally considered disinhibitory: Activation of the first inhibitory neuron can remove the ongoing inhibitory influence onto the output neuron from the middle inhibitory neuron. However, in the mouse direction-selective circuit, plasticity in a serial inhibitory microcircuit can preserve motion-evoked inhibition of the output neuron in the presence of visual noise (*46*, *74*). Specifically, the output neuron of this circuit, the On-Off DSGC, acquires its direction selectivity primarily from directionally tuned inhibitory inputs from SACs (*75*). However, the GABAergic synapse between the SAC and the DSGC is prone to short-term depression (*45*, *46*): When SACs are constantly activated by visual noise in the background, the SAC-DSGC inhibitory synapse would undergo depression and potentially jeopardize null-direction inhibition of DSGCs for moving stimuli. Serial inhibition of neighboring SACs prevents this synaptic depression and preserves motion-evoked inhibitory signals from SACs to DSGCs against background noise (*74*). Mechanistically, the serial inhibition between SACs contributes to the suppressive surround of the SAC's receptive field (*46*, *76*). When a moving bar traverses a SAC's receptive field, background noise activity of the SAC is transiently suppressed by neighboring SACs when the bar moves through the receptive field surround (*46*). Suppression of SAC noise activity immediately before its motion-evoked activation is a preventive mechanism against depression of the SAC-DSGC synapse in response to motion. When the SAC receptive field surround is weakened by genetically removing SAC-SAC inhibition, noise activity of SAC triggers depression of the subsequent motion response at the SAC-DSGC synapse and reduces DSGC direction selectivity in noisy motion background (*46*).

This alternative algorithm of serial inhibition is based on generalizable properties that are likely applicable to other serial inhibition microcircuits in the brain (*77*). In general, for a synapse that is prone to depression, it is beneficial to preserve its synaptic strength for relevant incoming signals while permitting depression for nonrelevant ones, e.g., "noise." This form of selective gating of relevant signals can be implemented by the specific temporal sequence of inhibitory neuron activation and is distinct from the commonly studied "gating by disinhibition." When the middle inhibitory neuron is activated by nonrelevant inputs, synaptic depression of the second inhibitory synapse can contribute to noise resilience of the output neuron (Fig. 4A). However, when the middle inhibitory neuron is activated by relevant

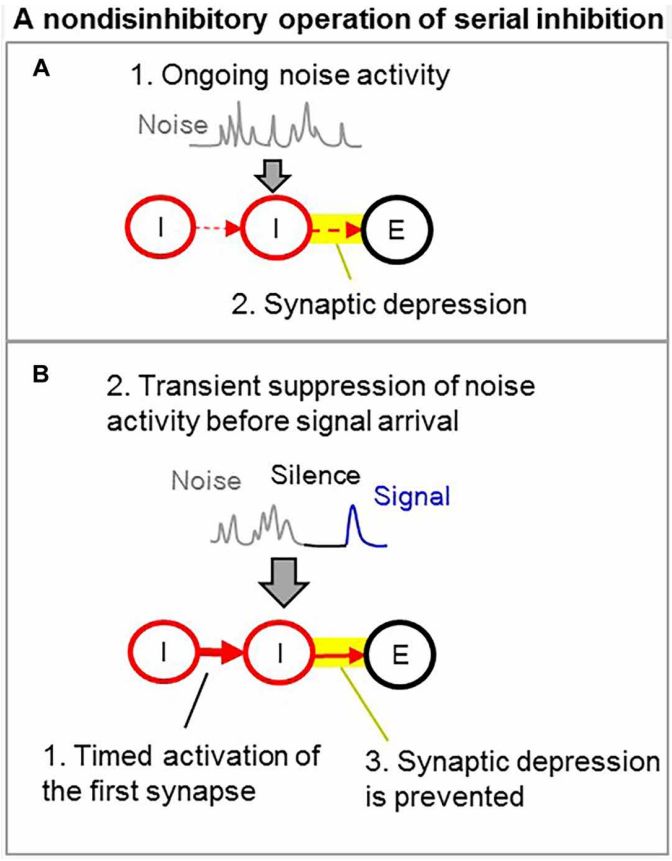


**Fig. 4. A gating function of serial inhibition as an alternative to disinhibition.** Short-term synaptic depression can lead to distinct signal transformations by a serial inhibition motif based on different patterns of network activity (**A** and **B**). Yellow shade indicates the locus of synaptic plasticity.

inputs, synaptic depression of the second inhibitory synapse to the output neuron can be prevented by timed activation of the first inhibitory neuron (Fig. 4B). That is, as an alternative to the disinhibitory effect, the first interneuron in the serial inhibition motif can preserve the output neuron's inhibitory inputs at specific time windows and contribute to noise resilience of the circuit, as exemplified in the SAC-SAC-DSGC motif in the retina. Given the prevalence of short-term plasticity, serial inhibition motifs elsewhere in the brain likely exhibit similar context-dependent algorithmic flexibility.

### Stimulus-dependent excitatory/inhibitory balance

When plasticity occurs at a synapse earlier in the network, the end effect can be remarkably sophisticated after the subsequent transformation steps in the circuit. A compelling example is in the primate cone signaling pathway to On parasol ganglion cells. The very first cells in the circuit, cone photoreceptors, undergo dynamic adaptation as the intensity of the visual stimulus changes in timescales of milliseconds to seconds. The adaptive signaling from cones is then conveyed to On and Off cone bipolar cells, which drive the rest of the circuit to produce excitatory and inhibitory inputs to On parasol ganglion cells, respectively. Different types of visual stimuli, for example, contrast reversing gratings versus natural images, activate the cones in different spatiotemporal patterns and thus generate distinct adaptive states in the cone population (*78*). This stimulus-dependent adaptation states of cones produce different excitatory/inhibitory (E/I) balances in On parasol cells, making them integrate spatial patterns of visual inputs nonlinearly for contrast-reversing gratings due to a periodic temporal window of dominating excitation over inhibition but linearly for natural images due to a more balanced E/I in the ganglion cell (Fig. 5) (*78*). This example again demonstrates that dynamic gain changes at individual synapses can profoundly change the computational algorithm of a circuit according to its input pattern.

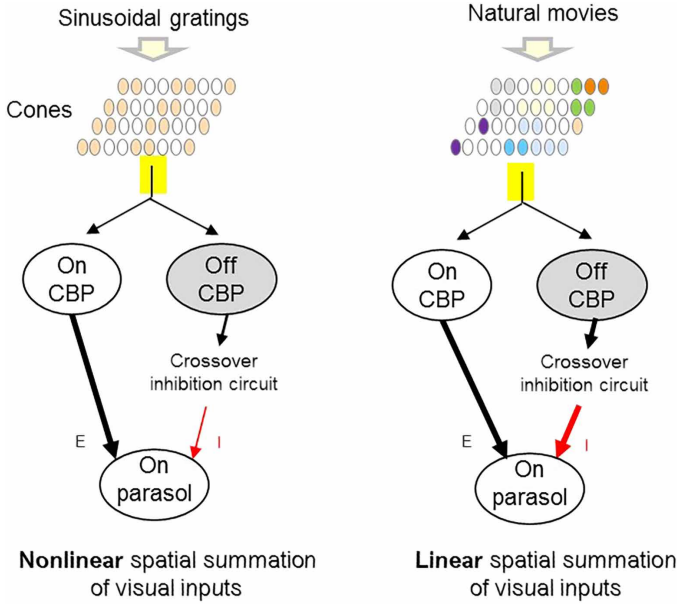


**Fig. 5. Dynamic adaptive states of cone photoreceptors induced by distinct stimuli affect E/I balance of output neurons.** Different colors in cones indicate their different adaptive states depending on the spatiotemporal pattern of the stimulus. Yellow shade indicates the locus of plasticity. CBP, cone bipolar cell.

## SUMMARY AND OUTLOOK

Studies of synaptic plasticity in retinal circuits offer a glimpse of the profound impact of this synapse-level phenomenon on circuit function. At only a few synapses downstream of the plasticity locus, plasticity's effects on signal transformation often become exceedingly complex because of the interactions between plasticity rules with diverse factors such as network dynamics and cellular properties. Future studies on integrating plasticity into the algorithmic operations of neural circuits will benefit from a multifaceted approach:

1) Delineating the relationship between physiological input patterns and changes in synaptic strength.

2) Exploring the stimulus space to identify ethologically relevant network dynamics and the forms of plasticity they recruit.

3) Obtaining a comprehensive wiring diagram of the circuit with functional and connectomic mapping.

4) Monitoring signal transformations at intermediate and end points of the circuits downstream of the plasticity locus.

5) Computational modeling for interpreting and predicting signal transformation in the network that eludes intuition and for constructing generalizable models across circuits.

In addition to plasticity mechanisms discussed in this review, synaptic strength can also be controlled by diverse neuromodulatory mechanisms, many of which are still poorly understood in the retina [reviewed in (*5*)]. Progress in understanding the mechanism and impact of neuromodulation at the synapse level will open new directions in linking dynamic signaling at individual synapses to context-dependent circuit function.

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