

Retinal encoding of natural scenes

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ABSTRACT

An ultimate goal in retina science is to understand how the neural circuit of the retina processes natural visual scenes. Yet, the vast majority of studies in laboratories have long been performed with simple, artificial visual stimuli, such as full-field illumination, spots of light, or gratings. The underlying assumption is that the features of the retina thus identified carry over to the more complex scenario of natural scenes. As the application of corresponding natural settings is becoming more commonplace in experimental investigations, this assumption is being put to the test and opportunities arise to discover processing features that are triggered by specific aspects of natural scenes. Here, we review how natural stimuli have been used to probe, refine, and complement knowledge accumulated under simplified stimuli, and we discuss challenges and opportunities along the way towards a comprehensive understanding of the encoding of natural scenes.

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INTRODUCTION

The sense of vision has evolved to solve the challenges encountered by animals in the visual environment. Thus, natural visual scenes provide the most essential stimulus context under which the neurons and neural circuits of the visual system operate. And it is this mode of operation and the processes required to solve natural visual tasks that are of primary interest to vision researchers. The challenge is, of course, that natural scenes are complex with intricate structure on a wide range of spatial and temporal scales. Light levels and spatial contrast can vary drastically in different regions of the same image, object boundaries create sharp transitions in brightness and color information, whereas surface textures and illumination gradients provide smoothly varying components. Temporal dynamics add further complications in the form of moving objects and self-motion, including eye movements, as well as alterations in illumination conditions.

In the vertebrate visual system, the first neural stage that has to deal with the complex, multi-faceted structure of natural scenes is the retina, a thin sheet of neural tissue at the back of the eyeball. It is among the most investigated parts of the nervous system, and a great deal of anatomical and physiological detail has been revealed about its sensory transduction mechanisms, its immense diversity of neuron types, and their responses to light. This vast background knowledge and the immediacy with which the visual stimulus acts on this neural system make it a great target for studying the encoding of natural scenes and for evaluating how the visual system copes with different aspects of the natural environment.

Yet, even for the retina, taking the full complexity of natural scenes into account seems daunting. It is thus no surprise that much of vision research has been guided by a reductionist strategy of separating visual processing into smaller, manageable chunks. The separation may be into specific tasks (e.g., to detect a luminance change or a motion signal, to efficiently transmit information) or into specific stimulus features (temporal contrast, periodic spatial structure, uniform motion, color, etc.). This divide-and-conquer strategy has had undeniable success, from general characteristics of receptive fields to specific computations ascribed to individual ganglion cell types.

The hope is, of course, that the understanding of the stimulus encoding, of the visual tasks that are solved, and of the circuit mechanisms hold up also for natural stimuli. To turn hope into certainty, there is a growing interest in the retina field to re-evaluate classical concepts – originally derived with simple, artificial stimuli – under natural stimulation. Moreover, one may expect that challenging the retina with natural scenes may reveal response patterns or mechanisms beyond those that are observed with traditional artificial stimuli.

Here, we consider three ways in which natural stimuli have been used to analyze signal processing in the vertebrate retina and discuss the insights and challenges that have emerged in recent years (**Figure 1a**). Perhaps most famously, the *normative perspective* seeks to determine what retinal features are needed to best solve a specific visual task in the context of natural stimuli. From the *coding perspective*, natural stimuli are used to inspect the structure and information content of activity patterns in individual or populations of retinal neurons. Finally, the *circuit perspective* employs natural stimuli to ask which circuit mechanisms shape the neuronal responses under natural conditions. All three perspectives rely

on appropriately designed computational models and selected natural stimuli, which brings us to the question of what choices there are to make when exploring how the retina encodes visual scenes.

FROM RECEPTIVE FIELDS TO COMPUTATIONAL MODELS OF RETINAL ENCODING

The retina's neural network is among the most intensely studied parts of the nervous system, and the basic layout and processing pathways are comparatively well understood (Cajal 1893; Masland 2001; Wässle 2004). Incoming light signals are captured by the photoreceptors, which pass on their signals via excitatory bipolar cells to the output neurons of the retina, the retinal ganglion cells (**Figure 1a**). In between, two classes of interneurons, horizontal cells and amacrine cells, provide feedforward, feedback, and lateral inhibition to gate and shape the signal transmission. Finally, the action potentials ("spikes") generated by the ganglion cells, travel down the cells' axons in the optic nerve to inform a multitude of brain regions about the natural visual world (Martersteck et al. 2017; Morin & Studholme 2014). Despite the long history of intense research, the retina has not ceased to surprise researchers with new insights about its complexity and signal processing capabilities. Recent years have seen a steady increase in the number of identified cell types, which may now be converging to well above a hundred neuron types for the mouse retina (Yan et al. 2020). These include roughly 40 type of ganglion cells (Baden et al. 2016; Bae et al. 2018; Tran et al. 2019), each providing a separate information channel over the entire visual field, and a staggering diversity of more than 60 types of amacrine cells (Yan et al. 2020). The functional role of most of these individual cell types as well as of the diversity as a whole has remained unclear and is arguably among the most fundamental riddles of early-vision research. Investigating retinal processing in the context of complex, natural stimuli will likely be needed to reveal the full functional potential embedded in this diverse and interconnected circuit.

Early investigations of stimulus encoding by the retina were unimpeded by this daunting hidden complexity and made good headway with simple stimuli, such as light spots that were flashed onto different retinal locations (Barlow et al. 1957; Hartline 1938; Kuffler 1953). This led to the distinction of ON and OFF cells and the fundamental description of the center-surround receptive field, which still dominates the functional picture of the retina today. Ideas of more complex stimulus encoding then arose with the observation of ganglion cell sensitivity to specific visual patterns, such as small dark, moving spots for the "bug perceivers" described by Lettvin et al. (1959), and of nonlinear spatial integration, as revealed by frequency doubling in response to contrast-reversing gratings (Enroth-Cugell & Robson 1966; Victor & Shapley 1979).

These early findings were cast into computational models of retinal processing, which still form the backbone of current analyses of the encoding of natural scenes. The most fundamental concept here is to regard the receptive field of a ganglion cell as a spatial filter through which the cell processes the scene to determine the level of its activity (Rodieck 1965). Higher similarity between filter and visual stimulus corresponds to stronger activation. By supplementing the filter with a time course, one obtains a spatiotemporal filter (**Figure 1b**), which can be applied to dynamic stimuli. This basic filtering operation underlies the perhaps most widely used model of neural stimulus-response relationships, not only in the retina, the linear-nonlinear (LN) model. After the linear filtering (the "L" in the LN model), a nonlinear transformation (the "N") connects the neuron's activation to its spiking output, typically the firing rate or spike probability for a given image or brief time period in the case of spatiotemporal input, such as a

natural movie (**Figure 1c**). In this way, the nonlinearity can capture effects of spiking threshold, response gain, and firing-rate saturation (Chichilnisky 2001). The LN model, together with its many extensions that are obtained, for example, by incorporating multiple parallel filters or feedback modules (McFarland et al. 2013; Pillow et al. 2008; Real et al. 2017) forms a powerful data analysis framework with a good compromise of biological interpretability and computational simplicity. Analyzing the encoding of natural scenes by the retina has relied heavily on this model framework by finding optimal model parameters (normative perspective), deciphering the messages that different response components carry about certain visual features (coding perspective), or identifying crucial model components and their biological counterparts (circuit perspective).

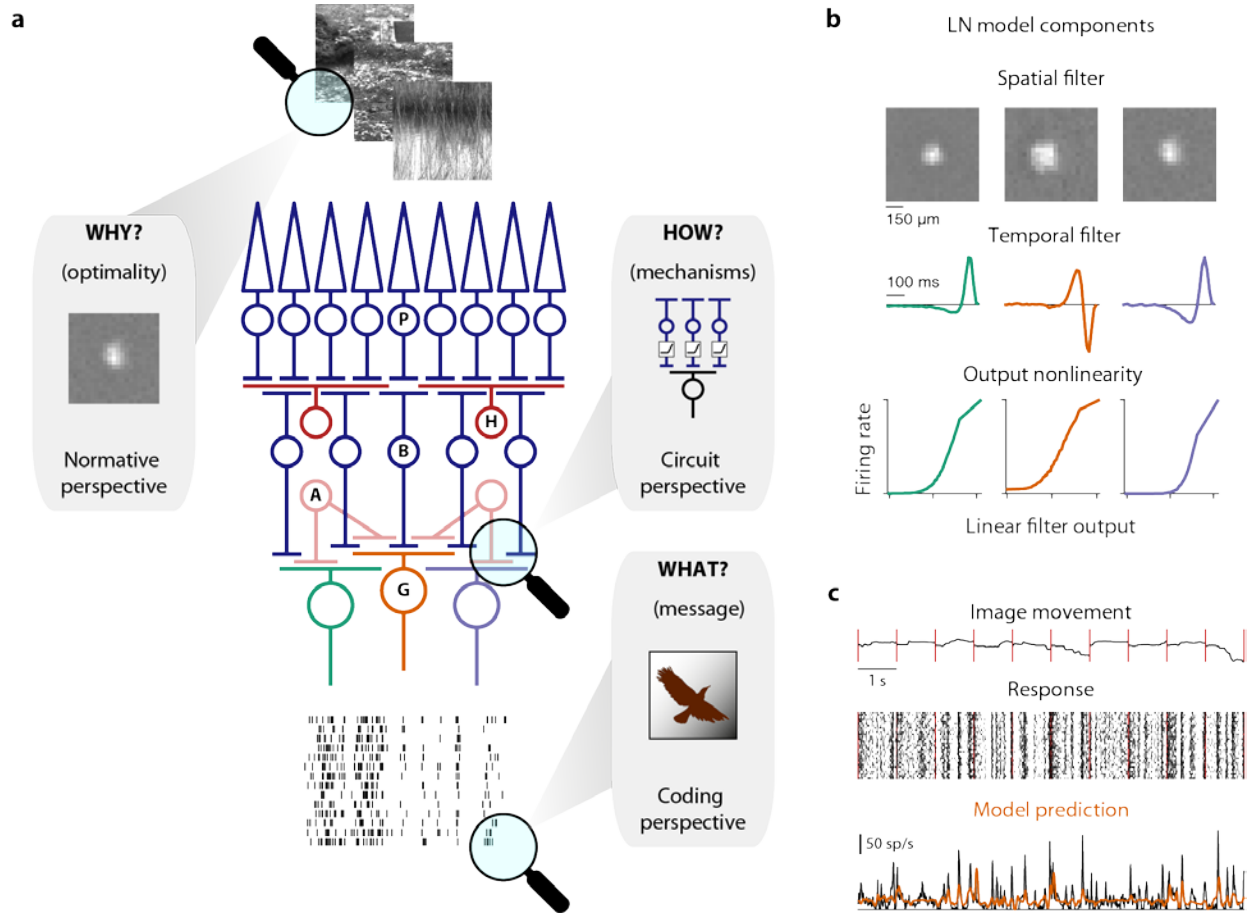


Figure 1. Three perspectives on retinal encoding of natural scenes. (a) Center: Schematic, simplified circuit of the retina with photoreceptors (P) and the excitatory bipolar (B) and ganglion (G) cells. Inhibition is provided by the horizontal (H) and amacrine (A) cells. Around: Schematic representation of the three perspectives under which natural stimuli are used in retinal research. (b) LN model components for three mouse ganglion cells of different types. (c) Spike raster (center) and corresponding firing rate (bottom) of the second cell in b to a naturalistic movie, constructed by shifting natural images on the retinal surface (top, red lines mark image switches). The LN model prediction is shown in orange.

NORMATIVE PERSPECTIVE

An early focus for studying the encoding of natural scenes was the question in what sense the retina might be specifically adapted to handle natural stimuli. By assuming that evolution shaped the retina to optimally cope with the visual structure of the environment, one can investigate how the retina *should* operate to achieve this optimality. This *normative perspective* thereby seeks to answer *why* certain features of the retina are the way they are, i.e., what functional role they play in the encoding of natural stimuli. The typical working agenda has been to identify a plausible optimality criterion (or “objective function”), formalize retinal signal processing in a modeling framework, optimize the model parameters to maximize the objective function in the context of natural input signals, and compare the identified optimal parameters to the anatomical and physiological features of the retina. What makes the retina so amenable to this approach are the immediacy of stimulus encoding with no prior neural stage of preprocessing and the fairly good knowledge that we have about its basic circuitry, which allows for specific comparisons of theory and experiment (Balasubramanian & Sterling 2009).

A typical starting point for the normative approach is the idea of *efficient coding*, which posits that a sensory system should maximize the information contained in its output signals (Attneave 1954; Barlow 1961). For retinal encoding of natural scenes, this means that retinal ganglion cells should not simply encode raw light intensity in their receptive fields because neighboring locations in visual space tend to have similar intensities (Field 1987) and neighboring cells would thus spend their action potentials largely on redundant information. A maximally efficient code, on the other hand, should let different ganglion cells encode independent bits of information, leading to uncorrelated retinal activity. This *redundancy reduction* (Attneave 1954; Barlow 1961) from correlated natural scenes to uncorrelated neural activity was formalized in a spatial filter model of retinal processing (Atick & Redlich 1990, 1992) and found to yield filters with center-surround structure (**Figure 2a**), whose surround strength depends on the level of noise in the system (**Figure 2b**). The filters display a striking resemblance with recorded receptive fields, and the filtering matches psychophysical measurements of human contrast sensitivity under different light levels (Atick & Redlich 1992). An alternative, though closely related view of center-surround receptive fields comes from the idea of *predictive coding* (Srinivasan et al. 1982). Here, the surround is viewed as using the light-intensity correlations of natural images to predict the illumination in the center, so that the ganglion cell encodes only deviations from this prediction and thereby optimally uses its dynamic range.

The established connection between center-surround receptive fields and the statistics of natural stimuli is arguably one of the highlights in the convergence zone of theoretical and experimental neuroscience and continues to shape investigations of natural stimulus encoding. Many follow-up studies have confirmed, extended, and refined this view, with different model frameworks and optimization strategies (Jun et al. 2021; Karklin & Simoncelli 2011; Lindsey et al. 2019; Ocko et al. 2018; Roy et al. 2021). The retinal mechanisms of redundancy reduction, however, might go beyond center-surround filtering, as nonlinear thresholding of filtered signals provided the larger contribution to the decorrelation of salamander retinal ganglion cells (Pitkow & Meister 2012).

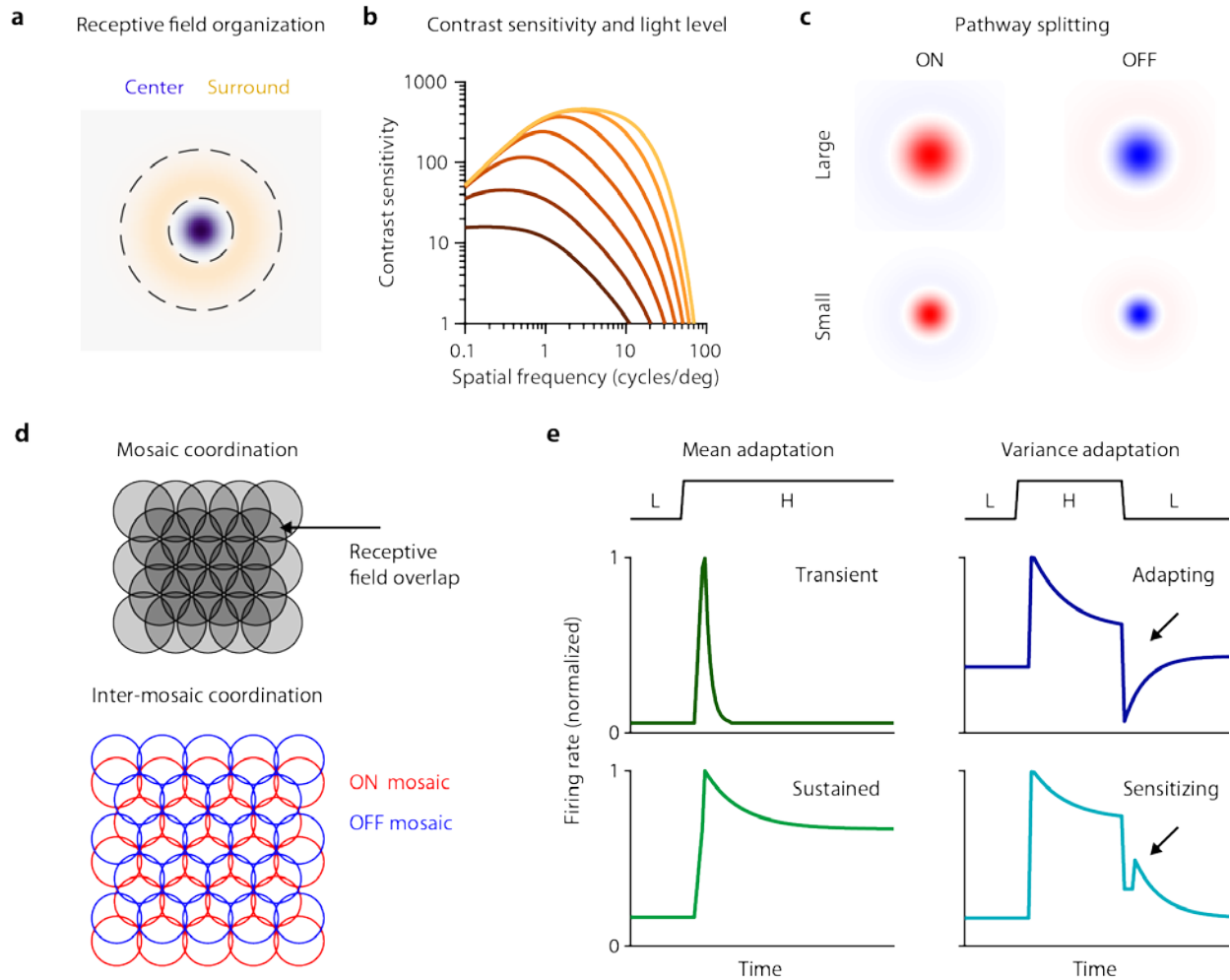


Figure 2. Normative perspective: Retinal features explained through efficient coding of natural scenes. (a) Schematic depiction of a center-surround receptive field. (b) Efficient-coding predictions of contrast sensitivity curves for different relative noise levels, corresponding to different background light levels (lighter shades denote lower noise/brighter light), following the calculations of Atick & Redlich (1992). The stronger bandpass filtering at brighter light results from a relatively stronger surround component. (c) Efficient coding can predict two types of pathway splitting: ON/OFF, and large/small, as depicted here by schematic receptive fields. (d) Top: Coordination of the receptive-field mosaic of a single ganglion cell type, illustrating receptive-field overlap. Bottom: Schematic depiction of anti-aligned ON and OFF-ganglion cell receptive-field mosaics, with receptive field overlap reduced for clarity. (e) Schematic response curves under steps from low (L) to high (H) mean luminance (left) and under steps between low and high contrast of flickering light (right). Different coding strategies predict transient or sustained response types for luminance steps and adapting or sensitizing response types for contrast steps, and arrows mark the response differences after returning to low contrast.

The principle of efficient coding in the context of natural scenes has also been used to explain the emergence of parallel pathways in the retina, such as the splitting of the neuronal population into ON and OFF cells (Gjorgjieva et al. 2014; Karklin & Simoncelli 2011) as well as into cells with small and large receptive fields (Ocko et al. 2018), matching, for example, the midget and parasol pathways of the

primate retina (**Figure 2c**). Furthermore, OFF cells are often smaller and more densely packed than corresponding types of ON cells, as observed in rat, macaque, and human retinas (Chichilnisky & Kalmar 2002; Kling et al. 2020; Ravi et al. 2018; Soto et al. 2020), which may reflect the predominance of OFF-type contrast in natural scenes (Ratliff et al. 2010). Populations of both ON and OFF receptive fields tightly tile visual space (**Figure 2d**, top), with an overlap that is found to be optimal for encoding natural images (Borghuis et al. 2008). Additionally, the receptive field midpoints of ON cells tend to show up in between those of OFF cells (**Figure 2d**, bottom), and the anti-alignment of the two mosaics contributes to optimal information transmission for natural images (Roy et al. 2021), though the optimality of this anti-aligned configuration appears to depend on the noise level in the system (Jun et al. 2021).

Natural stimuli contain correlations not only over space, but also over time, and the often bandpass temporal filtering of retinal ganglion cells, analogous to their center-surround receptive fields, can serve to reduce temporal redundancy (Dan et al. 1996; Pitkow & Meister 2012). Moreover, the natural visual environment is highly dynamic and entails large shifts in mean illumination and contrast (Rieke & Rudd 2009), for example, when saccades shift the gaze direction between regions of direct illumination and shade or between textures and object boundaries. The retina adapts to new light and contrast levels, and efficient coding theory can explain some of the observed phenomena of adaptation (Młynarski & Hermundstad 2021; Yedutenko et al. 2020). A model-based investigation of the decoding of dynamic natural stimuli (Młynarski & Hermundstad 2021) proposes that transient and sustained responses to step increases in luminance reflect optimal solutions to different decoding tasks (**Figure 2e**, left) and also captures the dependence of adaptation time scales on stimulus switching periods (Wark et al. 2009). In the same fashion, the model also suggests a similar task-specific optimality of cells that display either increased or decreased sensitivity after a switch to lower-contrast stimulation (**Figure 2e**, right), known as sensitization and adaptation, respectively (Appleby & Manookin 2019; Kastner & Baccus 2011).

Including not only luminance information but also chromatic statistics of natural images furthermore allows the derivation of color-opponent receptive fields (Atick et al. 1992; Doi et al. 2003), as observed in the midget pathway of the primate retina. For the mouse retina, on the other hand, it has been argued that chromatic encoding may require considerations beyond an efficient coding framework (Abballe & Asari 2021). The two cone types of the mouse retina, S-cones and M-cones, which are most sensitive to UV and green light, respectively, are inhomogeneously distributed across the retina, with S-cones dominating the ventral and M-cones the dorsal retina (Applebury et al. 2000; Szél et al. 1992). Though originally thought to be an adaptation to the prevalence of UV light coming from the sky and green light from the ground (Gouras & Ekesten 2004), it seems that the nonlinear responses of S-cones and their larger gain compared to M-cones make this configuration a near optimal detector for the natural distribution of achromatic contrast (Baden et al. 2013). Additionally, the spectral statistics of UV and green in a mouse's upper visual field (Qiu et al. 2021) may explain why green-UV color opponency is more pronounced in the ventral retina (Szatko et al. 2020). Similar task- and environment-specific adaptations of photoreceptor distributions and signals have been found for the zebrafish retina where UV-sensitive cones in a fovea-like spot on the retina support prey detection (Yoshimatsu et al. 2020) and signals from red- and green-sensitive cones already separate the chromatic content of natural daylight into achromatic and spectrally opponent components (Yoshimatsu et al. 2021).

Despite their undeniable successes, normative approaches often resemble post hoc explanations, deriving known features of the retinal circuitry under plausible, yet particular assumptions, such as the modeling framework, the objective function, and the metabolic cost or channel capacity (Sterling & Laughlin 2015). It is not always clear to what degree the derived optimal features remain robust to alterations in these assumptions. The level of assumed noise, for example, can lead to fundamentally different optimal retinal architectures (Jun et al. 2021). Some experimental evidence may also question the redundancy reduction assumption of efficient coding, as retinal responses retain considerable redundancy under natural stimuli (Pitkow & Meister 2012; Puchalla et al. 2005).

CODING PERSPECTIVE

Studying the retina under the normative perspective typically starts with specific assumptions about what visual information is encoded, such as the spatial distribution of light levels across a scene, as well as about how this information is represented, e.g., by the firing rates of individual ganglion cells. Yet, what visual features retinal ganglion cells encode is also an empirical question, which needs to be viewed in the context of natural stimuli, giving rise to the *coding perspective*.

Before we dive into the topic of how the neural code of the retina is experimentally studied with natural scenes, let us note that the concept of a *neural code* (or relatedly of *neural representation* of sensory information) is riddled with difficulties of what it means to encode or represent certain information. For the neural activity X to encode or represent some visual feature Y , should we just expect X to correlate with Y ? Or to somehow allow the (nonlinear) extraction of information about Y ? Or to be causally related to behavioral responses to Y ? Here, however, we put these important considerations aside and loosely speak of encoding when relevant information about Y is “readily available” and could “easily” (e.g., linearly) be read out from X by downstream circuitry, in line with the typical and practical use of “encoding” in the retina literature. In any case, we need to ask whether the encoding of a specific visual feature depends on the context of visual stimuli and whether findings obtained under simplified artificial stimuli need to be revised when considering natural scenes.

Direction-selective retinal ganglion cells, for example, are considered to encode the direction of visual motion because the cells respond strongly to spots of light or visual gratings that move in a particular direction (the preferred direction), but not for motion in the opposite (null-) direction (Barlow & Hill 1963). So a cell’s activity apparently encodes motion direction, as the motion component along the preferred/null-axis can be fairly well determined from the evoked activity – at least in the context of the moving spots or gratings (**Figure 3a**). Natural stimuli, on the other hand, display much more complex combinations of spatial contrast and motion and may also activate direction-selective ganglion cells through light intensity changes that occur independently of motion or even through motion in the null-direction. This problem is partly mitigated by inhibition from the receptive field surround, which reduces light-intensity-related activity under natural stimulation (Im & Fried 2016). Nonetheless, despite the clear response properties of a direction-selective ganglion cell under simple motion stimuli, its encoding under natural scenes can be ambiguous. The relative activity of multiple direction-selective ganglion cells, however, can still robustly and unambiguously encode motion direction (**Figure 3b**; Kühn & Gollisch 2019). This suggests that a population code may help extract complex information from natural scenes, such as translatory and rotatory self-motion (Sabbah et al. 2017).

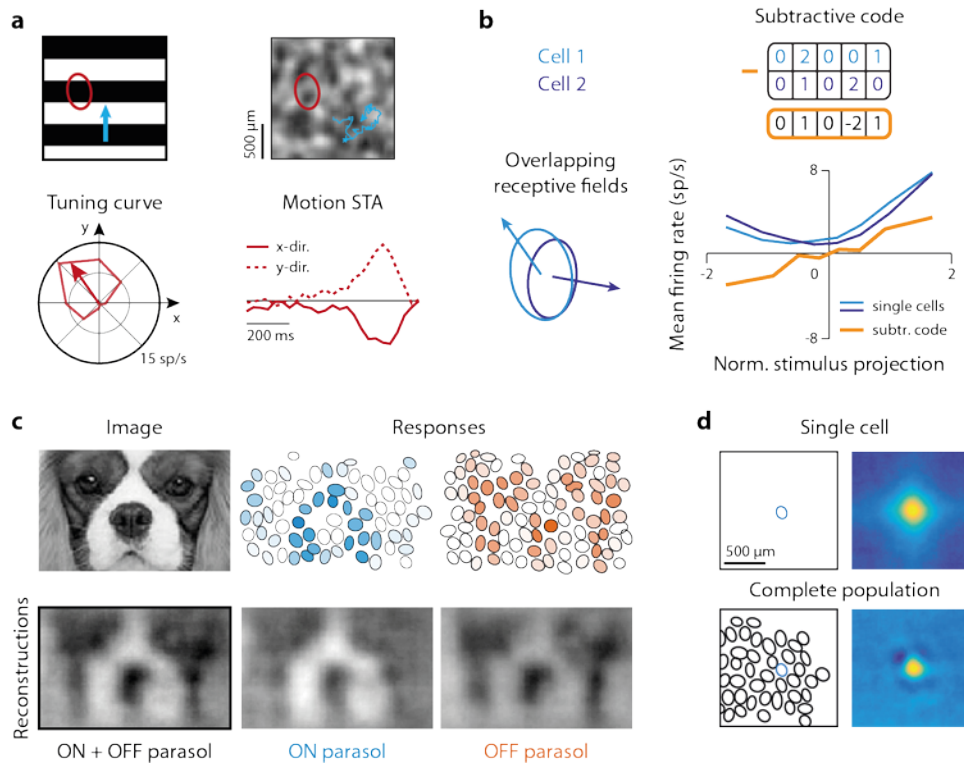


Figure 3. Coding perspective: The retina's messages about natural stimuli. (a) Comparing direction selectivity under drifting gratings (left) and textures moving similarly to fixational eye movements (right). The preferred direction under texture motion is obtained from the spike-triggered average of the motion steps in x and y direction (bottom right; data from a salamander direction-selective cell) and matches the preferred direction under drifting gratings for the sample cell (bottom left). (b) Ambiguity of direction encoding by single cells and resolution by a population code. Single direction-selective cells (blue) show elevated activity for motion along the preferred (positive stimulus projection) as well as the null direction (negative stimulus projection). The response difference (orange), on the other hand, depends monotonically on motion direction. Panels a-b adapted from Kühn & Gollisch (2019), licensed under CC BY 4.0. (c) Reconstruction of a natural image (top left) from responses of populations of ON and OFF parasol ganglion cells (top center and right; ellipses are receptive fields and saturation of color indicates elicited activity). Bottom row shows (left to right) reconstructions using both populations, using only ON, and using only OFF cells. (d) Optimal spatial reconstruction filters for a parasol ganglion cell taken in isolation (top) and from a joint decoding by a complete population (bottom). Panels c-d adapted from Brackbill et al. (2020), licensed under CC BY 4.0.

Even the simple notion that a ganglion cell encodes spatial contrast within its receptive field is worth scrutinizing, as the spatial correlations of natural stimuli lead to correlations of a cell's activity with light levels far outside the receptive field. Here, again, considering populations of neurons help clarify the matter, as reconstructions of natural images from spike counts of entire populations of primate ON and OFF parasol cells (Figure 3c,d) works best when the contributions of individual cells actually reflects the cells' center-surround receptive field structure (Brackbill et al. 2020). Interestingly, decoding finer spatial details of natural images is possible by going beyond a linear decoder that considers individual filter-like contributions from each cell and incorporating nonlinear decoding techniques (Kim et al. 2021;

Parthasarathy et al. 2017), suggesting that the temporal structure of ganglion cell spike patterns contains information about natural images beyond what is available through the cells' trial-averaged firing rates (Kim et al. 2021).

An aspect of natural stimuli that may be particularly suited to reveal new aspects of stimulus encoding is the frequent occurrence of rapid shifts in gaze direction, either through saccadic eye movements or movements of the head or body (Land 2015). The rapid succession of fixated images, interspersed by fast, global motion signals might trigger modes of signal processing that remain untapped during artificial stimuli such as white noise or temporally isolated flashes. Indeed, simulated saccades can provoke strong ganglion cell activity or suppress it (Amthor et al. 2005; Idrees et al. 2020; Noda & Adey 1974; Roska & Werblin 2003). Yet, which aspects of the combination of pre- and post-saccadic image are encoded by ganglion cell activity across a saccade remains an open question for most ganglion cell types and is difficult to predict from response properties derived with isolated image presentations. For example, specific cells in the mouse retina displayed an unexpected sensitivity to recurring images across saccades (Krishnamoorthy et al. 2017).

Another important context for the encoding of a visual stimulus is given by the background on which it is presented. Different natural scenes provide different background, and a recent study found that the spatial sensitivity profile of salamander and mouse ganglion cells indeed depends on the background image (Goldin et al. 2021). ON-OFF ganglion cells may even invert their relative sensitivity to positive and negative contrast depending on the context-defining image. This context dependence of the preference for brightening or darkening can be viewed as an encoding of absolute contrast relative to the background image (Goldin et al. 2021).

Apart from asking what visual features are encoded by specific retinal ganglion cells, natural stimuli have also been used to study the structure of ganglion cell population activity in near-natural conditions. A particular focus has been to assess the prevalence and importance of correlated firing within ganglion cell populations (Nirenberg et al. 2001) and the statistical structure of multi-neuronal activity patterns (Ganmor et al. 2015; Schneidman et al. 2006). Relating multi-neuronal activity patterns to specific aspects of natural stimuli, however, has remained an open question, though certain stimulus features, which are part of natural viewing, may trigger synchronous activity, such as fixational eye movements (Greschner et al. 2002; Masquelier et al. 2016) and motion reversal (Schwartz et al. 2007).

CIRCUIT PERSPECTIVE

While the normative and coding perspectives aim at answering *why* the retina is designed the way it is and *what* is actually encoded by different patterns of ganglion cell activity, we also strive to understand *how* the retina actually implements the signal processing that underlies its coding schemes. Which elements of the neural circuitry are involved in a given encoding, which connections, which cellular properties and synaptic dynamics? These questions address the retina from a *circuit perspective* and have traditionally been targeted with simple, custom-made stimuli, aimed at isolating a particular phenomenon of interest. For example, flashed or flickering light spots can be used to investigate response kinetics, surround inhibition, as well as light and contrast adaptation. Focusing on these simple stimuli, however, leaves open two important questions: 1) Do the identified mechanisms act in the same way under natural stimuli, when stimulus statistics are different and when different types of mechanisms act simultaneously? 2) Do we miss specific mechanisms because they are not triggered under the commonly used artificial stimuli?

To cope with the complexity of naturalistic stimulation and still relate elicited responses to specific circuit features, the circuit perspective heavily relies on computational modeling and inference about the circuitry through parameter fitting. Typically, this involves cascade-type models, composed of mathematical primitives, such as filters, nonlinear transformations, and additive or multiplicative feedforward and feedback interactions. These components have been used to encapsulate various concepts from retinal physiology, such as the spatial receptive field (Brown et al. 2000; Chichilnisky 2001), adaptation to luminance and contrast (Jarsky et al. 2011; Ozuysal & Baccus 2012), spike generation (Weber & Pillow 2017), specific inhibitory interactions (Baccus et al. 2008; Geffen et al. 2007; Roska & Werblin 2003), or neuronal couplings (Meytlis et al. 2012; Pillow et al. 2008), and serve as an expedient tool to bridge artificial and natural stimulus scenarios. The models reside in a sweet spot of computational simplicity for fitting to experimental data combined with sufficient complexity to allow for biological interpretations. Enlarging this sweet spot through computational and experimental advances remains a hot and important topic for studying retinal function.

Spatial integration

A retinal mechanism that has recently received much attention because of its importance for the sensitivity to spatial contrast under natural stimuli is the pooling of bipolar cell inputs by ganglion cells. Simple models, such as the LN model, often consider the spatial integration over the excitatory bipolar cell inputs in the receptive field center to be linear, as reflected by the linear spatial filtering that forms the first model stage. Yet, many ganglion cells throughout various retinal model systems display nonlinear spatial integration under contrast-reversing spatial gratings (Bölinger & Gollisch 2012; Carcieri et al. 2003; Demb et al. 1999; Enroth-Cugell & Robson 1966; Petrusca et al. 2007), the stimulus that is classically used to investigate spatial stimulus integration (**Figure 4a**).

The lack of nonlinear spatial integration in common filter-based models has been hypothesized to contribute to the often unsatisfactory performance of these models under natural stimuli (Gollisch 2013; Heitman et al. 2016; Schwartz & Rieke 2011). It is not *per se* clear, however, that nonlinear signal transmission from bipolar to ganglion cells is actually relevant under natural stimuli. First, the gratings

typically applied to identify these nonlinearities have high contrast and lack concomitant low spatial frequencies, thus making ganglion cell responses sensitive to even tiny nonlinear contributions. Second, due to the spatial correlations of natural images, the receptive field center may only rarely be filled with patches of high spatial contrast, for which the nonlinearities matter most. And third, the typically periodic presentation of reversing gratings might drive adaptive mechanisms into a non-natural regime.

To test for the relevance of nonlinearities, several studies compare model predictions to ganglion cell responses under natural stimuli. Depending on cell type, accurate as well as inaccurate response predictions are observed (Cao et al. 2011; Heitman et al. 2016; Karamanlis & Gollisch 2021; Liu et al. 2017; Nirenberg & Pandarinath 2012; Turner & Rieke 2016). Additionally, subunit models with rectified input nonlinearities, representing the nonlinear signal transmission of bipolar cells as seen under artificial stimuli (Borghuis et al. 2013; Demb et al. 2001), can improve the prediction accuracy for many cells, highlighting the importance of nonlinear spatial integration also under natural stimuli (Liu et al. 2017; Shah et al. 2020; Turner & Rieke 2016). The cell-type specificity of nonlinear spatial integration under natural stimuli was also demonstrated by comparing ganglion cell responses under natural images and under homogenous spots of the same mean luminance (Turner & Rieke 2016) and by comparing responses under luminance-matched pairs of natural images (Karamanlis & Gollisch 2021; Liu & Gollisch 2021). Turner & Rieke (2016), for example, observed that OFF parasol cells were sensitive to spatial structure under natural stimuli, and their nonlinear spatial integration stems directly from their rectified excitatory inputs. ON parasol cells, on the other hand, were found to integrate inputs linearly under natural stimuli, despite their nonlinear spatial integration under reversing gratings (**Figure 4b**). This finding exemplifies that – at least for some cell types – insights from artificial stimuli may not easily generalize to natural stimuli.

Nonlinearities upstream of the bipolar-to-ganglion cell synapse may also contribute to natural scene encoding. Bipolar cell membrane potentials in the salamander retina show nonlinear contrast encoding and even nonlinear integration of photoreceptor signals under both artificial and natural stimuli (Schreyer & Gollisch 2021). And photoreceptors themselves can display pronounced nonlinear contrast encoding, especially when challenged with the broad range of light levels occurring in natural stimuli (Endeman & Kamermans 2010; Howlett et al. 2017), which effectively drives the phototransduction mechanism into its nonlinear regime (Clark et al. 2013; van Hateren 2005) and triggers adaptation mechanisms that contribute to photoreceptor nonlinearities (Angueyra et al. 2021; Howlett et al. 2017). In the mouse retina, nonlinear encoding of contrast in photoreceptors is particularly pronounced in S-cones, which may be a specific adaptation to the naturally occurring distribution of contrasts in the upper visual field (Baden et al. 2013). For the retinal encoding of natural scenes, the observed photoreceptor and bipolar cell nonlinearities may lead to sensitivity to spatial structure even below the scale of bipolar cell receptive fields.

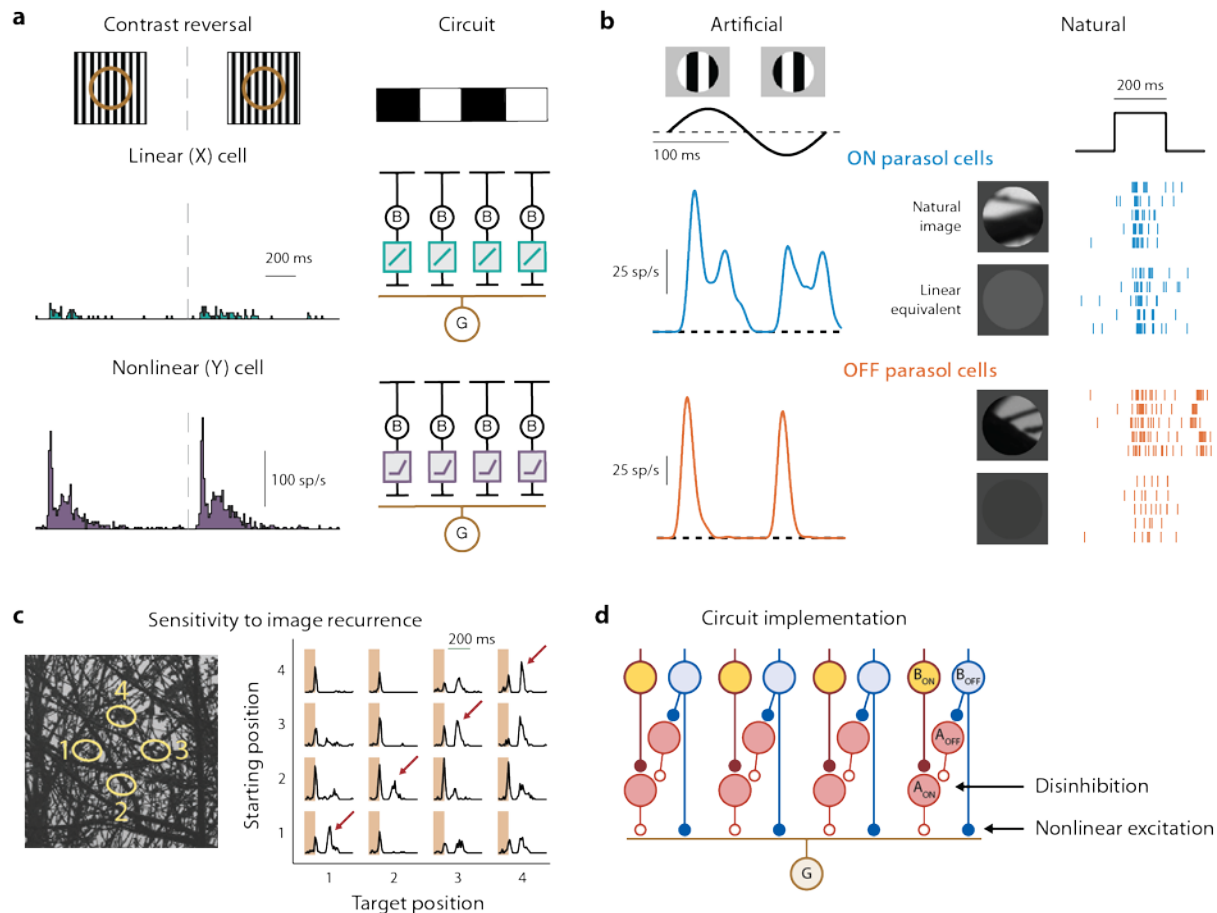


Figure 4. Circuit perspective: Neural circuitry involved in processing natural stimuli. (a) Responses of X and Y mouse retinal ganglion cells to reversing gratings (left) and corresponding circuit models (right) with linear and rectified transmission, respectively, from bipolar cells (B) to the ganglion cell (G). Adapted from Karamanlis & Gollisch (2021), licensed under CC BY 4.0. (b) Left: Responses of macaque ON and OFF parasol cells to reversing grating, showing frequency doubling indicative of nonlinear integration. Right: Responses to natural images and to homogenous spots of the same mean luminance (linear equivalent), indicating nonlinear spatial integration for OFF, but not ON cells. Adapted from Turner & Rieke (2016), Copyright (2016), with permission from Elsevier. (c) Responses of a mouse ganglion cell sensitive to image recurrence under saccade-like shifts of natural images. Left: Image with receptive field outlines for four fixation positions. Right: The cell's firing rate profiles for all transitions. The starting and target positions are the fixation positions before and the after the shift. The shaded regions mark the transition. For equal starting and target position, the image shifted to the central position and then returned. Red arrows mark firing rate peaks under recurring image position. (d) Circuit mechanism explaining image-recurrence sensitivity. The ganglion cell receives excitation from OFF bipolar cells and inhibition from ON amacrine cells. The ON amacrine cells are themselves inhibited by OFF amacrine cells, leading to disinhibition of the ganglion cell. Panels c-d adapted from Krishnamoorthy et al. (2017), licensed under CC BY 4.0.

Adaptation

The wide ranges of luminance and contrast levels encountered in natural scenes (Frazor & Geisler 2006) challenge the retina to continuously adjust its limited dynamic range (Rieke & Rudd 2009). Adaptation to mean luminance is thought to arise primarily from calcium-dependent feedback in the phototransduction process (Matthews et al. 1988; Nakatani & Yau 1988) and is classically studied by presenting probe flashes on a steady illumination background. Contrast adaptation, on the other hand, is thought to first occur in bipolar cells or in the transmitter release at their synaptic terminals (Baccus & Meister 2002; Manookin & Demb 2006) and is often investigated under noise-like flicker of light intensity with sudden changes in variance. The distinct sites of luminance and contrast adaptation appear to fit the idea that the two should occur independently, as luminance and contrast levels in natural scenes were also found to be independent of each other (Mante et al. 2005). Yet, some components of luminance adaptation appear to arise downstream of photoreceptors at the bipolar cell output (Dunn et al. 2007; Jarsky et al. 2011), creating a mechanistic overlap of the two adaptation processes. Furthermore, under stimulation with the wide range and skewed distribution of natural light intensities (Endeman & Kamermans 2010; van Hateren et al. 2002), a contrast-adaptation-like mechanism can also be observed in goldfish photoreceptors, triggered by voltage-dependent hyperpolarization-activated ion channels (Howlett et al. 2017). In primate photoreceptors, using naturalistic light intensity sequences with saccade-fixation dynamics, Angueyra et al. (2021) observed adaptation components fast enough to adjust responses during fixation periods of few hundred milliseconds. This rapid adaptation has also important consequences for the balance of excitatory and inhibitory inputs to ganglion cells under natural stimuli (Yu et al. 2021), which appears to contribute to the discrepancy in spatial stimulus integration between natural stimuli and contrast-reversing gratings in ON parasol cells discussed above (Turner & Rieke 2016).

Inhibition

The perhaps least understood and most mysterious aspect of the retinal circuitry is the multitude and diversity of inhibitory interneurons, especially the more than 60 types of amacrine cells (Yan et al. 2020), which provide inhibition to ganglion cells, to bipolar cells, and to each other. These interactions likely play particular roles for natural scene encoding, which may therefore hold a key to solving the mystery of retinal inhibition. Inhibitory pathways are important, for example, in the context of gaze shifts, which provide global, coherent stimulation to the entire retina. Indeed, global saccade-like shifts of natural scenes activate retinal inhibition (Roska & Werblin 2003; Sivyer et al. 2019), which may contribute to saccadic suppression of visual perception. Furthermore, inhibition triggered by saccade-like shifts may not only suppress responses, but also shape post-saccadic activity through disinhibitory interactions (Geffen et al. 2007; Krishnamoorthy et al. 2017). For certain cells in the mouse retina (Krishnamoorthy et al. 2017), such disinhibition through serial connections of glycinergic and GABAergic amacrine cells leads to a particular sensitivity for the recurrence of spatial patterns across a saccade (**Figure 4c,d**), which may be relevant for correcting fixational drift through microsaccades.

Other inhibitory circuit features were identified via motion stimuli derived from natural scenarios, though the actual stimuli were simplified and schematized. The so-called object-motion-sensitive ganglion cells, for example, may help detect moving objects in the presence of eye-movement-induced

background motion, owing to their specific sensitivity to relative motion (Ölveczky et al. 2003), whereas global motion signals are suppressed by inhibitory signals from polyaxonal amacrine cells in the surround (Baccus et al. 2008). Similarly, looming-sensitive ganglion cells in mouse were found to strongly respond to approaching, but not lateral motion (Münch et al. 2009). This stimulus selectivity has given rise to a circuit model with local cross-over inhibition, potentially from All amacrine cells (Münch et al. 2009), but looming-sensitive excitatory input from glutamate-releasing amacrine cells has also been implicated as a circuit mechanism (Kim et al. 2020). Targeted ablation of these amacrine cell specifically diminishes the defensive response of mice to overhead looming (Kim et al. 2020), thus suggesting a direct role of amacrine cell processing in visual behavior.

Activation of the receptive field surround is typically thought to provide response suppression. Yet, Turner et al. (2018) showed that the surround can also modulate the spatial integration properties of the receptive field center under natural stimuli. This is caused by a shift from nonlinear to more linear transmitter release at the bipolar cell synapse when surround signals depolarize the bipolar cell. To account for such surround effects that occur before input integration in the ganglion cell, circuit models with subunits that have their own antagonistic surrounds could help improve predictions of ganglion cell responses to natural stimuli (Enroth-Cugell & Freeman 1987; Turner et al. 2018).

Towards a complete model – Lego versus Michelangelo

Being able to predict ganglion cell responses to any natural stimulus by a model that represents the retina's neural circuitry and properties of its elements would be an ultimate goal of the circuit perspective. Achieving this goal will require an elaborate model containing the components discussed here and potentially more: integration over multiple bipolar cells, adaptation to light and contrast at the local and global scale, and inhibitory interactions that suppress or gate different information channels. Which road should we pursue towards such a complete model? Can we investigate the individual building blocks in isolation by custom-made stimuli and put them together like a set of Lego bricks? The potential of such an approach for predicting responses to natural stimuli has yet to be tested. An obvious challenge, however, comes from potential interactions between these building blocks. If, for example, the nonlinearity of spatial integration in the receptive field center depends on mean luminance (Grimes et al. 2014) or on activation of the surround (Turner et al. 2018) or if adaptation depends on the organization of a receptive field into subunits (Brown & Masland 2001; Garvert & Gollisch 2013; Khani & Gollisch 2017), studying these building blocks in unison is called for.

As an alternative, one may hope to set up a modeling framework that contains all the potential components and interactions and then extract the relevant elements and their parameters *en bloc*, like Michelangelo uncovering his David hidden in a single slab of marble. However, the challenge of optimizing the many parameters of such an intricate, nonlinear model seems daunting. While complex fits of cascade models designed to match retinal circuits are feasible (Maheswaranathan et al. 2018a; Real et al. 2017), they have yet to be attempted under natural stimuli. More abstract models in the style of artificial neural networks, on the other hand, have already been used to capture ganglion cell responses to natural scenes (Goldin et al. 2021; Maheswaranathan et al. 2018b; McIntosh et al. 2016). As an approach for studying retinal mechanisms in the context of natural stimuli, artificial neural networks may include circuit motifs that represent actual retinal elements (Turner et al. 2019), and it is

possible to extract such motifs from networks trained on retinal responses to natural scenes (Tanaka et al. 2019).

CONCLUDING REMARKS

The topic of retinal encoding of natural scenes comprises many facets, including the questions why retinal signal processing is structured the way it is, what aspects of natural scenes are encoded by different retinal information channels, and how the retinal circuitry extracts and processes this information. Early insights about the relationship between ganglion cell receptive fields and natural scene statistics (Atick & Redlich 1992) still relied on findings from the retina made with simple, artificial stimuli. As technical limitations are overcome, probing the retina with actual naturalistic stimuli has turned from possible to routine over recent years. These experimental measurements are needed to sample the circuit in regimes that may have previously been unexplored and to test whether concepts derived under artificial stimulation still hold for naturalistic settings.

Analyzing retinal responses under natural stimuli will continue to heavily rely on computational models to cope with the complexity of the stimulus-response relationship. It will be necessary to explore model structures that can encompass the growing knowledge about relevant circuit mechanisms and remain computational tractable. Incorporating nonlinear input from bipolar cells, for example, is typically approached with subunit models, but may need to be extended to incorporate input from different types of bipolar cells, adaptive properties of bipolar cells, or surround and substructure of bipolar cell receptive fields. The inhibitory surround may require its own subunits (Takeshita & Gollisch 2014) and be supplemented with inhibitory effects beyond the classical receptive field surround, acting on large spatial scales (Baccus et al. 2008; Jazdzinsky & Baccus 2015; Manookin et al. 2015) or locally shaping signal transmission in the receptive field center (Szatko et al. 2020). And considering chromatic image content brings in an additional stimulus dimension with its own intricate interactions (Joesch & Meister 2016; Khani & Gollisch 2021; Szatko et al. 2020). The appropriate model structure is not only important for parameter fitting under the coding or circuit perspective, but also for defining the space of potential operations in which to search for optimal designs under the normative perspective. For example, rather than a single nonlinearity, normative approaches may profit by modeling retinal nonlinearities at multiple stages, which have been shown to display an information-boosting effect (Gutierrez et al. 2021).

Besides shaping the modeling framework, attention should be given to selecting the set of natural stimuli to be used in the investigations. For focusing on the encoding of spatial structure, flashing photographed images is often the approach of choice, and databases of calibrated and versatile natural images are readily available (Olmos & Kingdom 2004; Tkačik et al. 2011; van Hateren & van der Schaaf 1998). But flashed photographs, of course, lack natural temporal dynamics. Instead, movies of natural scenes can be used. Their temporal dynamics may, for example, be governed by the camera or environmental movement (Betsch et al. 2004; Salisbury & Palmer 2016) or emulate self-motion trajectories from saccades and fixational eye movements (Heitman et al. 2016; Roska & Werblin 2003; Segal et al. 2015; Turner & Rieke 2016).

Paying justice to all dynamics is a tremendous challenge, however, and it is unlikely that a one-size-fits-all natural stimulus exists. It seems likely that some retinal neurons, ganglion cells as well as amacrine cells, are triggered best by rare, but important visual features, which may not be frequent enough to substantially impact responses under generic natural scenarios. In the original characterization of the W3 ganglion cell in the mouse, for example, a striking feature was the cell's lack of spiking to what could be considered a generic natural stimulus, and the cell only revealed its functional characteristics when probed with specifically chosen isolated motion objects (Zhang et al. 2012). Other neurons may require certain types of saccade-like shifts (Krishnamoorthy et al. 2017), combinations of object motion and fixational eye movements (Ölveczky et al. 2003), or small moving objects (Jacoby & Schwartz 2017) to reveal their full processing potential. Thus, a useful set of natural stimuli should strive to not only match the overall statistics of natural scenes, but also cover specific features and feature combinations that could be of particular importance.

Insight about the importance of visual stimulus features and the structure of natural visual stimuli in behaviorally important circumstances is now increasingly generated by studies of naturalistic behavior and concomitant sensory processing (Holmgren et al. 2021; Kim et al. 2020; Wallace et al. 2013). Fortunately, sharing data from such behavioral experiments, such as eye-movement traces appears to be common practice among vision science labs. An even greater benefit might be obtained if the use of natural stimuli could be more standardized by jointly casting available insight about natural scenes and visual behavior into a unified set of natural stimuli, covering different aspects of visual dynamics and visual tasks. This would allow different labs to probe different parts of the retinal circuitry – and perhaps also other visual areas of the brain – with the same natural stimuli for easier comparability and generalizability. This could be analogous to the versatile “chirp stimulus” (Baden et al. 2016), which is emerging as a standard artificial stimulus to characterize temporal response properties of visual neurons.

Let us finally also note that natural stimuli will not replace the application of custom-made simple, artificial stimuli. These still hold tremendous potential when teasing out specific aspects of signal processing while minimizing confounding effects from other dynamics in the system (Rust & Movshon 2005). Studying signal processing under constant mean light intensity or contrast, for example, has been a standard to minimize adaptation effects. In particular, hybrid stimuli that retain some aspects of natural stimuli while simplifying others have turned out very useful for identifying candidate retinal functions and related mechanisms. Examples also discussed in this text include natural time courses of light intensity and chromatic components with no spatial structure (Angueyra et al. 2021; Endeman & Kamermans 2010; Howlett et al. 2017; van Hateren et al. 2002), static presentations of natural photographic images (Brackbill et al. 2020; Cao et al. 2011; Karamanlis & Gollisch 2021; Turner & Rieke 2016; Turner et al. 2018), and eye-movement dynamics with simplified spatial patterns (Idrees et al. 2020; Krishnamoorthy et al. 2017; Kühn & Gollisch 2019; Ölveczky et al. 2003). Finding a good balance of naturalistic stimulus patterns and artificial simplifications and subsequently identifying the right natural stimuli for testing whether the hybrid-stimulus results generalize to truly natural scenarios will be among the critical steps towards a comprehensive understanding of retinal encoding of natural scenes.

SUMMARY POINTS

1. Investigating retinal processing with natural stimuli is becoming more commonplace to test findings from artificial stimulation and to search for new functional properties specific to certain natural scenarios.
2. Computational models of the retinal circuit provide important tools for handling the complexity of natural stimuli when studying retinal stimulus encoding.
3. Retinal encoding of natural scenes can be viewed from the normative perspective, asking why retinal features are the way they are, the coding perspective, asking what is encoded by activity patterns of different retinal ganglion cells, and the circuit perspective, asking how retinal processing shapes responses under natural scenes.
4. The normative perspective combines a traditional focus on explaining receptive field structure and new successes regarding cell-type diversity, adaptation, and arrangement of retinal mosaics.
5. Under the coding perspective, natural and hybrid stimuli are used to study the messages contained in the spiking output of the retina. Here, population codes may help establish robustness of coding concepts derived from simple stimuli against the additional variability and complexity under natural stimuli.
6. The circuit perspective focuses on investigating the mechanisms that shape retinal responses under natural scenes, re-evaluating the role of known circuit features and providing opportunities to discover new mechanisms, triggered by specific components of natural stimuli.

FUTURE ISSUES

1. How does the efficient coding hypothesis relate to complex signal processing beyond the single-filter models, including, for example, nonlinear integration, adaptation, or inhibition?
2. How can we probe and refine our understanding of the retina's neural code with natural stimuli? How do findings derived with artificial stimuli about the encoding of specific visual features, like object motion or looming, generalize to natural scenes?
3. How can we study inhibitory interactions with natural stimuli? How can we incorporate inhibition beyond surround suppression into computational models?
4. How can we combine different computational models of specific operations (adaptation, nonlinear signal pooling, inhibitory interactions) into a single, holistic model for processing of natural stimuli?
5. Is it feasible to set up and fit a holistic model of retinal processing to responses under natural scenes and retain biological interpretability?
6. Which natural or hybrid stimuli could serve as a standard stimulus set to probe diverse retinal functions and circuit operations in order to boost generalizability and comparability across laboratories and investigated cell types?

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The authors declare no competing interests.

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