Information processing in the outer retina of fish
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Chapter 1

General introduction

Function of the retina
The retina translates light into neuronal activity. Thus, it renders visual information of the external environment. The retina can only send a limited amount of information to the brain within a given period. To use this amount optimally, light stimuli are strongly processed in the retina. This processing entails extraction of useful information from a visual scene, while ignoring redundancies. Here for, the retina consists of a several cell types organized in different layers, each with distinct contributions in processing visual information. The main topic of this thesis is concerned with the question how the first layers of neurons, the outer retina, are involved in the processing of visual information.

In the current chapter, I will introduce the neural elements, which constitute the vertebrate retina and describe how they are involved in processing light stimuli. I will try to sketch a general picture of the buildup and functioning of the retina, but will remark on specific features of the retina of fish occasionally, since these animals were test subjects in the studies I have conducted. However, I will begin with a description of light itself.

The nature of light
Light is electromagnetic radiation, which is visible to the human eye (see Figure 1). It consists of packets of electromagnetic waves called photons. The wavelength of its electromagnetic energy determines whether a photon is visible. Our eyes can detect electromagnetic energy of wavelengths between around 400 and 700 nm.
The natural source of light on earth originates mostly from stars, like the sun, which emit a relatively flat wavelength distribution of radiated power in the visible range (see Figure 2, black line). About 42%\(^1\) of the sun's electromagnetic radiation power that reaches the earth’s surface is in the visible range. However, our eyes do not detect energy, but photons. Therefore, a more meaningful figure with regard to vision in the distribution of photons radiated from the sun reaching earth. This can be computed by converting the radiated power to radiated photons. One then finds that only around 26% of the photons received from the sun are in the visible range (Figure 2, red line). Moreover, there are about four fold more photons at the long wavelength end of the visible spectrum compared with the short wavelength end.

Intensity is a property of light that relates to the amount of photons arriving on a given surface within a given time. Within a single natural scene light intensities can differ about a factor ten thousand (4 log units). Between day and night, light intensities can change by a factor of about 1000 billion (12 log units, see Figure 3). It is no trivial task for the retina to remain responsive over this entire range of intensities and still be able to

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\(^1\) This is the percentage of irradiance between 400 and 700 nm relative to the total amount of solar irradiation between 280 and 4000 nm, available at http://rredc.nrel.gov/solar/spectra/am1.5/ (Gueymard \textit{et al}., 2002; Gueymard, 2004).
see fine details within a given scene. To cope with these conditions the retina adapts by using various intracellular, extracellular and network mechanisms.

Figure 2 Solar spectral irradiance for visible light. This graph depicts the amount of irradiance in terms of power (black line) and photons (red line) between 350 and 750 nm on a south facing surface with 37° inclination from horizontal. (Gueymard et al., 2002; Gueymard, 2004).

When light hits an object three things can happen: 1) the light can be absorbed 2) it can pass through an object, or 3) it can be reflected. Often two or all three of these occur. For many objects, the relative amount of light absorbed and reflected depends on the light’s wavelength. A green leaf of a plant, for instance, absorbs long- and short-wavelength light and reflects light of middle wavelengths, which we perceive as green. However, in contrast to wavelength, which is a physical property of light, color is a construct of our brain, and what color we see not only depends on wavelength content of the reflected light from the object, but also on that of the surround, and on the properties of our visual system.
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Figure 3 Differences in light levels and visual features at various light conditions. Adapted from (Stockman & Sharpe, 2006)

The eye

The retina is housed in the eye (see Figure 4). It is the function of the eye to keep a focused and clear image of the outside world projected onto the retina. The eye is positioned in its socket by six small extraocular muscles. These are organized in three pairs, with the muscles of each pair working in opposition, facilitating movements in one of the three direction planes.

Figure 4 Comparison of schematic sagittal sections of the human (Homo sapiens) and zebrafish (Danio rerio) eye. Taken from (Chhetri et al., 2014)
Both the cornea and the lens help to keep a focused image on the retina. In non-aquatic animals, about two-thirds of the refractive power (bending of the light) necessary for focusing takes place at the air-cornea interface, where the light enters the eye. The lens of the eye supplies the remaining one-third of the focusing power. Pulling or relaxing the ciliary muscles that surround it changes the shape of the lens to focus an image on the retina. Two other sets of muscles change the diameter of the pupil and thus adjust the amount of light entering the eye. Finally, the pigmented iris ensures that all light entering the eye passes through the lens and thus prevents stray light.

The eye of aquatic animals is adapted to vision in water and differs somewhat from non-aquatic species, as described above. Their cornea renders little refractive power underwater, because the refractive index of water is similar to that of the interior of the eye. Aquatic animals compensate for this lack of refraction at the cornea interface by having a much stronger, spherical lens. Focusing of an image on the retina is achieved by moving the lens back and forth with a refractory muscle. The pupil of these animals is rather fixed and the lens protrudes through the pupil.

The retina

The retina is part of the brain. It has the shape of a plate, which is about 250 µm thick. Around the turn of the previous century, Ramón y Cajal was able to describe the principal architecture of the vertebrate retina using a silver staining technique developed by Golgi (see Figure 5). The vertebrate retina consists of three layers of nerve-cell bodies, the outer nuclear layer (ONL), the inner nuclear layer (INL) and the ganglion cell layer (GCL). Two layers containing synapses made by the axons and the dendrites of their cells separate these layers, the outer plexiform layer (OPL) and the inner plexiform layer (IPL). The distal part of the vertebrate retina contains the light-sensitive photoreceptor cells (PC). The cell bodies of the photoreceptors are located in the ONL. Protrusions of pigment epithelium (PE) cells envelope photoreceptor outer segments. PE cells support photoreceptor function by absorbing scattered light, regenerating visual pigments, supplying essential metabolites, and buffering extracellular ions amongst others. Photoreceptors transmit their signals to horizontal cells (HCs) and bipolar cells (BCs) via a specialized synaptic complex called a triad, located in the OPL. The subsequent layer, the INL, contains cell bodies of HCs, BCs and amacrine cells (ACs). HCs are involved in lateral feedback to photoreceptors in the OPL, whereas BCs
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longitudinally feed forward to ACs and ganglion cells (GCs). ACs are responsible for lateral communication within the IPL, contacting both BCs and GCs. The output units of the retina are the GCs, which are located in the ganglion cell layer (GCL). They transmit their signals to the brain via their axons, which are bundled in the optic nerve. The retina contains a single, stereotypical glia cell called the Müller cell (MC), which spans the full thickness of the retina. MCs have an extensive range of functions, which are vital for the functioning and health of retinal neurons, e.g. accumulating potassium from the extracellular space, taking up neurotransmitters such as glutamate, and offering an alternative pathway for the regeneration of visual pigment of cone photoreceptors.

Figure 5 Artistic impression of a sagittal section of the mammalian retina by Ramón y Cajal. In this drawing the principal architecture, cell types and layers of the retina can been seen.
Photoreceptors

Photoreceptors are the principal transducers of light in the retina. They consist of an outer segment, an inner segment, a nucleus and a synaptic terminal. Photoreceptors come in two types, rods and cones (see Figure 6). Classically, this distinction is based on morphology. Rods are long and slender. Cones are short and tapered. Physiologically, the most important difference between the two is in their relative sensitivity to light. Rods are sensitive to very dim light (even single photons). The light intensities at which they are responsive are called scotopic. Cones require much brighter light to respond and function in photopic conditions. There also is an intensity region in which both rods and cones are active termed the mesopic range.

Figure 6 Electron microscopical image of outer (o.s.) and inner (i.s.) segments of rod and cone photoreceptors of rhesus monkey. Insert depicts photoreceptor discs at a higher magnification. Taken from (Kolb, 1970).

Both rods and cones contain light-sensitive visual pigments in their outer segments, which are embedded in so-called disc membranes. Visual pigments consist of two parts: a chromophore and an opsin. The chromophore is the aldehyde of vitamin A and can and can come in two forms, retinal (vitamin A1) and 3-dehydroretinal (vitamin A2). Visual pigment can be constituted by combining an opsin with either a vitamin A1-, or A2-based chromophore. Consequently, there are two great families
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of visual pigments, rhodopsins, based on retinal from vitamin A1, and the porphyropsins based on 3-dehydroretinal from vitamin A2. Rhodopsins are found throughout the vertebrates, whereas porphyropsins are restricted to some amphibians, aquatic reptiles and teleosts, an infraclass of fish including goldfish and zebrafish.

Visual pigments are not equally sensitive to all wavelengths of light, i.e. they are more likely to absorb a photon of a certain wavelength compared to others. This phenomenon can be described by the absorbance spectrum of a pigment, which is the relative amount of absorbance as a function of the stimulus wavelength. Construction of photopigments with A2-based chromophores causes a shift to longer wavelengths of the absorbance spectrum compared to the A1-based photopigment.

![Figure 7](image)

**Figure 7** Action spectra of three types of goldfish cone photoreceptors. Taken from Palacios et al. (1998)

Depending on the species, cones can be of several types, each containing a different visual pigment. Goldfish have four types of cones, UV-cones, S-cones, M-cones, and L-cones. Their pigments are most sensitive to different wavelengths of light (see Figure 7), namely ultraviolet (360 nm), short- (455 nm), middle- (540 nm), and long-wavelength (625nm) respectively (Marks, 1965; Hárosi & MacNichol, 1974; Stell & Hárosi, 1976; Hárosi, 1976; Hawryshyn & Beauchamp, 1985; Bowmaker
et al., 1991; Palacios et al., 1998). These differences are the basis of color vision.

Photoreceptors respond to light through a process called bleaching. In this process, a molecule of visual pigment absorbs a photon after which it is changed in its conformational state and becomes activated. The activation of the pigment is the onset of a series of chemical reactions, called phototransduction (see Fig. 8), which is essentially similar in both rods and cones and culminates in the generation of a neuronal signal.

The visual pigment of the photoreceptors (R) consists of a transmembrane protein opsin, which is linked to a chromophore. Activated R (R*) is catalytically active and binds to a G-protein called transducin (T), which initiates a signal-amplifying cascade of reactions. In the inactive state, T is a membrane-associated complex consisting of αβγ-subunits and non-covalently bound GDP. Upon binding to R*, GDP is converted into

![Figure 8 Schematic overview of the phototransduction cascade. Taken from webvision.med.utah.edu by Wolgang Baehr.](image)
GTP. The α-subunit of T bearing GTP, $T_\alpha^*$, dissociates from $T_\beta_\gamma$ and activates membrane-associated phosphodiesterase (PDE).

In the dark, PDE is a complex composed of two catalytic (α and β) and two regulatory (γ) subunits. The interaction of PDE γ-subunits with $T_\alpha^*$ leads to the activation of phosphodiesterase (PDE*). PDE* in turn hydrolyzes cGMP into GMP and a proton. Photoreceptor outer segments possess membrane bound cation channels, which are gated directly by cGMP and control the influx of ions across the photoreceptor plasma membrane. In the dark, the cGMP concentration in the outer segment is high and these channels are open, which constitutes a dark current that partially depolarizes the photoreceptor cell to around -40 mV. The dark current is mainly composed of the influx of Na$^+$ (80%), however, a Ca$^{2+}$ component (15%) and a Mg$^{2+}$ component (5%) are also present (Yau, 1994). The influx of these ions into the outer segment is balanced by the efflux of K$^+$ cations via K$^+$-selective channels located in the inner segment. Meanwhile Na$^+$/K$^+$ pumps continue to pump Na$^+$ out and K$^+$ into the cell and thus maintain the chemical gradient for these ions. The hydrolysis of cGMP by PDE* leads to a change in cGMP-gated channel conformation and results in channel closure. Channel closure decreases the conductance of the plasma membrane to the cations constituting the dark current and consequently results in the hyperpolarization of the plasma membrane. The action spectrum of a photoreceptor describes the relative response size versus the stimulus wavelength. In chapter 2, the action spectra of zebrafish cones is described.

Calcium ions regulate several stages of the phototransduction pathway by modifying the activity of different Ca$^{2+}$-binding proteins, which in turn interact with key enzymes in the pathway. For instance, calcium ions are involved in the recovery of the dark state of photoreceptors through the regulation of guanylate cyclase (GC), the enzyme that catalyzes the conversion of GTP to cGMP. In the dark, the Ca$^{2+}$ concentration in outer segments is high, ~500 nM, and GC activity is low. After photoactivation, closure of the channels in the plasma membrane reduces the influx of cations, including Ca$^{2+}$. However, the cell’s Na$^+$/Ca$^{2+}$–K$^+$ exchanger continues to extrude Ca$^{2+}$, and as a result, the Ca$^{2+}$ concentration drops, activating GC to produce cGMP. The cGMP-gated channel is composed of two subunits (α and β) that form a symmetric heterotetramer. It is also responsive to the concentration of Ca$^{2+}$ and might be regulated by calmodulin (CaM). Recoverin (Rec) represents a third step in the phototransduction pathway that is sensitive to the concentration of Ca$^{2+}$. Rec lengthens the lifetime of R* at higher concentrations of Ca$^{2+}$, which
are associated with dark-adapted photoreceptors. Rec inhibits the phosphorylation of R* at high Ca\(^{2+}\) levels by direct binding to RK. These Ca\(^{2+}\)-sensitive steps represent the principle mechanisms of light adaptation in vertebrate photoreceptors. However, the most important adaptation process in photoreceptors is bleaching adaptation, which is due to a large amount of photoconverted pigment molecules. This caused less pigment to be available to absorb photons, which decreases sensitivity (for reviews of phototransduction and adaptation, see (Burns & Baylor, 2001; Fain et al., 2001; Arshavsky et al., 2002)).

Photoreceptors signal to HCs and BCs by releasing glutamate, which is controlled by the influx of Ca\(^{2+}\) through presynaptic voltage-gated calcium channels. In the dark, photoreceptors are depolarized, voltage-gated calcium channels are open, and glutamate is consequently continuously being released into the synapse (Murakami et al., 1972; Cervetto & Piccolino, 1974; Copenhagen & Jahr, 1989; Marc et al., 1990). In order to maintain high release rates, photoreceptors employ a specialized vesicle release apparatus called a ribbon. This is a flat organelle, which is anchored to the presynaptic membrane. Synaptic vesicles tie to both sides of the ribbon via short filaments. At the presynaptic membrane, they dock ready for release, which is triggered by the influx of calcium through voltage-dependent calcium channels, located in the presynaptic membrane. The ribbon seems to acts like a conveyor belt, on which vesicles are continuously being moved toward the presynaptic membrane.

**Horizontal cells**

Horizontal cells are located in the distal border of the INL, proximal to photoreceptors. They have flat cell bodies and large dendritic trees, located in narrow layers. HCs come in several subtypes, which can differ greatly from species to species. Goldfish has four types of HCs. One type receives input from rods only (rod driven), whereas three others types are exclusively connected to cones (cone driven). The cone-driven HCs can be classified based on their spectral sensitivity, i.e. responsiveness to light of different wavelengths (see Figure 9). Monophasic HCs (MHCs) hyperpolarize to light of all wavelengths, biphasic HCs (BHCs) hyperpolarize to short wavelengths and depolarize to long wavelengths and triphasic HCs (THCs) hyperpolarize to both short and long wavelengths and depolarize to middle wavelengths (MacNichol & Svaetichin, 1958; Norton et al., 1968). Cone driven HCs can also be classified based on their morphology as H1, H2 and H3 cells, which seems to correspond to the
spectral types, MHCs, BHCs and THCs respectively. H1 cells have large cell bodies and relatively small dendritic fields. H2 cells have smaller cell bodies but larger dendritic fields. H3 cells have the smallest cell bodies of the three but the most extensive dendritic trees.

**Figure 9** Connectivity of the different types of cone-driven HCs according to Stell et al. (1975).

There has been some debate concerning the connectivity of cones to cone-driven HCs in fish. Based on the presence and location of HC dendrites in cone synapses Stell et al. (1975) developed a model to explain the spectral sensitivity of the different types of cone-driven HCs. In this model, MHCs receive input from L-cones and feedback to all cone types, BHCs receive input from M-cones and feedback to S-cones, and THCs
receive input from S-cones. Later studies have shown this model to be inaccurate on several points. Firstly, MHCs receive input from M-cones (Yang et al., 1982, 1983; Tauchi et al., 1984; Joselevitch et al., 2010) in goldfish. Moreover, MHCs appear to make connections with all cone-types, including a fraction of the UV-cones in zebrafish (Klaassen et al., 2016). However, no contribution of UV-cones to MHCs and BHCs could be found in goldfish (Joselevitch et al., 2010). Secondly, the feedback signal measured in cones was found to be spectrally broad and non-opponent (Kraaij et al., 1998), whereas one would expect a change of sign of the feedback response in S-cones due to the feedback they receive from BHCs. Recently, it has been suggested that cone glutamate release can spillover to neighboring cones and, through glutamate transporter-associated chloride current, can modulate their output (Vroman & Kamermans, 2015). This would constitute an additional, non-HC mediated, feedback pathway, which might explain the spectral broadness and non-opponent nature of feedback as measured in cones.

The photoreceptor/horizontal cell synapse
As mentioned previously, photoreceptors form a specialized synapse together with its postsynaptic partners in a triad. This synapse consists of a large presynaptic photoreceptor synapse, which is invaginated by the dendrites of HCs and BCs (Stell, 1967). These dendrites end in close proximity of the photoreceptor synaptic ribbon. BCs terminate at a central position and HCs a lateral position relative to the ribbon. Both BCs and HCs express glutamate-receptors on their dendrites, making them sensitive to the neurotransmitter release from photoreceptors (Klooster et al., 2001).

HCs feed back to photoreceptors, which leads to a shift in the activation function of the photoreceptor calcium current. The mechanism that produces this shift remains a topic of debate. Classically it was assumed that this feedback-loop involved the release of GABA from HCs. The presence of GABA in the dendrites of HCs supported this assumption. However, blocking GABA-mediated transmission pharmacologically is does not reduce the feedback-induced shift of the cone calcium current (Verweij et al., 1996). Two alternative hypotheses propose that the shift is broad about by either acidification of the synaptic cleft (Vessey et al., 2005), which alters the open probabilities of calcium channels, or by an ephaptic mechanism (Byzov & Shura-Bura, 1986; Kamermans et al., 2001; Klaassen et al., 2011), which changes the voltage over the photoreceptor membrane as sensed by the presynaptic voltage-gated calcium channels. A
recent study suggests that these two mechanisms might in fact both be active on different timescales (Vroman et al., 2014). This leaves the role of GABA in the dendrites of HCs unresolved. In Chapter 5, we suggest an alternative function for GABA in the outer retina.

**Bipolar cells**

Based on anatomical evidence a multitude of morphologically distinct types of BCs can be identified depending on the species. In goldfish, 15 different types of BCs have been described (Sherry & Yazulla, 1993). These morphological types can be subdivided in two classes: mixed input BCs, which receive input from both rods and cones, and cone driven BCs, which exclusively receive input from cones. The receptive field of BCs display center-surround organization, meaning that the sign of their response when stimulated with an annulus of light is opposite to that of stimulation of its center. This feature is due to inhibitory feedback from HCs to cones.

BCs can be further separated based on the direction of their light-evoked response: OFF-BCs hyperpolarize upon light stimulation, and ON-BCs depolarize when stimulated. The difference in response direction between these two BC types is brought about by expression of different glutamate-receptors at their dendrites. OFF-BCs, express ionotropic AMPA-receptors, whereas ON-BCs express metabotropic glutamate receptors. AMPA receptors are both glutamate receptors and cation channels, which open in response to the binding of glutamate. While metabotropic glutamate receptors are G-protein coupled receptors, which after binding glutamate initiate a second-messenger cascade that ultimately leads to the closure of cation channels.

**Amacrine cells**

ACs form the most diverse group of cell types of the retina. There is little information on the amount of AC types in the goldfish. However, it has been found that the zebrafish might have at least 18 types (Connaughton et al., 2004), whereas in roach, a related teleost, they might be grouped in as many as 40 major types (Wagner & Wagner, 1988). In zebrafish, most ACs contain either GABA or glycine (Connaughton et al., 1999), and most seem to express ionotropic glutamate receptors (Yazulla & Studholme, 2001). Given the diversity of ACs a complete description of their roles is still

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missing, yet they appear involved in wide range of functions, such as
relaying rod signals, direction selectivity, and orientation selectivity.

**Ganglion cells**

GCs form the output units of the retina. Apart from a number of AC types,
they are the only cell type of the retina which fire action potentials. Like
BCs, GCs display center-surround organization. GCs can be subdivided in
many types, which each transmit a specific feature of a visual stimulus.
These features include contrast, spectral content and motion. Remarkably,
several GC types are also intrinsically photosensitive. These cells express
melanopsin as a visual pigment. However, their light response is very
sluggish and it is therefore believed that they are not involved in visual
image perception, but other tasks, like control of pupil size and as input for
the body’s central biological clock, the suprachiasmatic nucleus.

**Coding**

Neural coding is concerned with how sensory and other information is
represented by neurons. The main goal of studying neural coding is to
categorize the relationship between the stimulus and neuronal responses.
One way of looking at neural coding is by means of information theory.
Information theory provides a scheme in which one can investigate the
efficiency and reliability of communication. In principle, information
theory is applicable to any system in which a transfer of information takes
place. Likewise, the retina can be studied using information theory, as a
system which transmits information to the brain regarding amounts of light
falling onto its photoreceptors (Atick, 1992).

In information theory, any device, system or process that generates
messages as its output is generically referred to as an information source.
Sources represent their messages as combinations of symbols, often called
the source symbols. In the visual environment, these symbols are the
different grey levels of light pixels in the image mosaic. Natural
information sources do not generate random sequence of information, but
display a certain statistical structure in their message. In natural images this
can be appreciated in the similarity of light intensity and color of nearby
pixels. Changes in light intensity and/or color only change abruptly at edges
or borders and otherwise occur gradually in space (Atick, 1992).

In information theory, the medium transmitting or storing
information the information from the source is called the information
channel, which convey messages through a set of symbols termed channel
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symbols. One of the issues discussed in this thesis is how the source symbols are mapped into the channel symbols, known as the channel coding problem (Atick, 1992). Retinal neurons encode information using graded potentials, except for GCs and some ACs, which can fire action potentials.

Since there is a high degree of spatio-temporal and chromatic correlation among pixels in natural images, a pixel-by-pixel representation of natural scenes, which is the representation formed by the photoreceptor mosaic, is inefficient. Therefore, the nervous system invests some of its resources to recode incoming signals to improve efficiency. Coding strategies dealing with redundancies can be divided in minimum redundancy codes and minimum entropy or factorial codes (Atick, 1992). The first strategy aims to eliminate inefficiency due to non-uniform probability distributions of the input signal. The second strategy deals with correlations within the stimulus.

Minimum entropy or factorial codes can remove redundant information across a population of retinal neurons by making their responses statistically independent, i.e. any particular piece of information is not duplicated in several neurons. Light intensities of adjacent points in a natural visual scene are strongly correlated, making that the responses of adjacent photoreceptors are also strongly correlated. HC receive input from many cones and are therefore preferentially collecting this correlated signal. This correlated signal is fed back negatively to the cones, making that the size of the correlated signal in the output of the cones is strongly reduced. This is a form of minimum entropy redundancy reduction (Srinivasan et al., 1982).

The opponent processing of color by horizontal cells can be considered a way using a minimum redundancy reduction in the spectral domain. The spectral sensitivity of L-, M- and S-cones overlap substantially, creating highly correlated, statistically dependent, responses. Efficient coding can be achieved by transforming cone responses such that they become orthogonal, i.e. independent of each other. Buchsbaum and Gottschalk (Buchsbaum & Gottschalk, 1983) demonstrated mathematically that efficient information transmission can be achieved by transforming three correlated color mechanisms, representing signals coming from three types of cones, into three more or less independent channels: one achromatic (luminosity) and two spectrally opponent (chromatic) channels.

Previous studies, devoted to coding by retinal neurons, primarily made use of artificial stimuli, like discrete pulses and white noise. The last decade has seen more and more utilization of so-called natural (or
naturalistic) stimuli to study coding by retinal neurons. These kinds of stimuli are designed to mimic the image, which, under natural conditions, would fall onto the retina. Since the retina is tuned to deal with these kinds of stimuli, using them might reveal coding strategies, which remain obscure when applying artificial stimuli. In chapters 3 and 4, we have used such stimuli to examine the coding strategies of cone photoreceptors and HCs.

**Thesis outline**

This thesis deals with the coding of information in the outer retina in general and more specific the coding schemes employed when using natural stimuli.

   The spectral sensitivity of three cone types of the zebrafish are described in chapter 2.

   In chapters 3 and 4, we examine responses of cones and HCs to natural stimuli. We analyze the results from information theoretical perspective.

   The fifth chapter illustrates how cone chloride currents are involved in modulating the size of feedback from HCs to cones.

   In the final chapter, the main results are summarized and discussed.
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References


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