From Synapses to Circuits: Different Levels of Functional Modeling of the Retina

Dissertation

zur Erlangung des Grades eines

Doktors der Naturwissenschaften

der Mathematisch-Naturwissenschaftlichen Fakultät

und

der Medizinischen Fakultät

der Eberhard-Karls-Universität Tübingen

vorgelegt

von

Cornelius Schröder

aus Stuttgart, Deutschland

2022

Tag der mündlichen Prüfung:	3.2.2022
Dekan der Math.-Nat. Fakultät:	Prof. Dr. Thilo Stehle
Dekan der Medizinischen Fakultät:	Prof. Dr. Bernd Pichler
1. Berichterstatter:	Prof. Dr. Philipp Berens
2. Berichterstatter:	Prof. Dr. Thomas Euler
Prüfungskommission:	Prof. Dr. Philipp Berens
	Prof. Dr. Thomas Euler
	Prof. Dr. Jakob Macke
	Prof. Dr. Aristides Arrenberg

Erklärung / Declaration:
Ich erkläre, dass ich die zur Promotion eingereichte Arbeit mit dem Titel "*From Synapses to Circuits: Different Levels of Functional Modeling of the Retina*" selbständig verfasst, nur die angegebenen Quellen und Hilfsmittel benutzt und wörtlich oder inhaltlich übernommene Stellen als solche gekennzeichnet habe. Ich versichere an Eides statt, dass diese Angaben wahr sind und dass ich nichts verschwiegen habe. Mir ist bekannt, dass die falsche Abgabe einer Versicherung an Eides statt mit Freiheitsstrafe bis zu drei Jahren oder mit Geldstrafe bestraft wird.

*I hereby declare that I have produced the work entitled "*From Synapses to Circuits: Different Levels of Functional Modeling of the Retina*", submitted for the award of a doctorate, on my own (without external help), have used only the sources and aids indicated and have marked passages included from other works, whether verbatim or in content, as such. I swear upon oath that these statements are true and that I have not concealed anything. I am aware that making a false declaration under oath is punishable by a term of imprisonment of up to three years or by a fine.*

Tübingen, den ....
Datum/Date Unterschrift/Signature

Hello, World!

Abstract

The retina is a popular model system in neuroscience and its processing of visual information has been studied in great detail. However, a lot of functional properties like adaptational processes or circuit level computations remain poorly understood. One example is color vision which has only been studied in detail in mammals but is little explored for other vertebrates. For a complete understanding of a neuronal system it is the gold standard to cover all Marr's levels of explanation (implementation, algorithm and computation). Yet this is challenging as it often requires utilizing a variety of experimental, analytical and modeling approaches. This challenge is also reflected in existing functional models of retinal activity, which often focus on the algorithmic model, like models of system identification. These models lack a clear biologically interpretable implementation compared to detailed mechanistic models, and can not easily reveal the performed computations. In addition, linking complex neural models to experimental data becomes challenging, especially if the aim is to draw conclusions about the inferred model parameters.

In this thesis, I present models for different neuronal mechanisms in the retina and how they can be fitted to experimental data. I show how abstract models of system identification can be enhanced by biological plausible components to replicate adaptational processes, to make the models biologically more interpretable and to allow for *in silico* experiments which are otherwise not possible. In a second line of research I show how processing in the retina is differentially tuned depending on the position in the eye. On the example of UV photoreceptors in zebrafish I present behavioral, anatomical and functional differences, as well as synaptical tuning properties to highlight features of the visual signal. In a final study, I investigate color processing at the first retinal stage in zebrafish, and how it is linked to efficient coding principles for color vision. Throughout the presented work, I exploit the framework of simulation based inference to link experimental data to the computational models by additionally providing uncertainty estimations.

In summary, in this thesis I present an approach to fill the gap between black-box and detailed biophysical modeling which can be a powerful tool to provide detailed explanations spanning from a functional to an implementational level. Additionally, I show in integrative studies of UV and color processing in cones how a system can be precisely understood by carefully covering different levels of explanation. To link the experimental data to computational models I showcase the potentials of simulation based inference in neuroscience, and how neuroscience can profit from recent developments in machine learning.

List of Abbreviations

ABC	Approximate Bayesian Computation
AC	Amacrine Cell
AZ	Acute Zone
BC	Bipolar Cell
BCN	Bipolar Cell Network
DNN	Deep Neural Network
EM	Electron Microscopy
GC	Ganglion Cell
HC	Horizontal Cell
MCMC	Markov Chain Monte Carlo
MEA	Multi-Electrode Array
PCA	Principal Component Analysis
PR	Photoreceptor
SBI	Simulation Based Inference
SI	System Identification

Table of Contents

Introduction

Our perception of the world is highly shaped by the visual input we receive. Vision is maybe the most important sense for humans as well as for many other species. It starts in the retina, which is a thin neural tissue at the back of the eye and acts as a light detector and processor for visual stimuli. The retina is an exceptional model system in neuroscience since experimentalists can control the input to the system and have developed various techniques to read out information from all its different neuronal layers. The retina has been studied in great detail and although the overall architecture is settled, many mechanisms and processing steps remain poorly understood (Masland, 2001; Baden et al., 2018).
To understand the processing of the visual signal, its representation in the neural system and the performed computations, it is crucial to develop accurate models of the underlying system. Models can help to formalize ideas; they can distill the current knowledge, and test and produce new hypotheses. In addition, models can provide explanations for observed phenomena and help to gain understanding for complex processes. For the retina, these models can range from a molecular to cellular to network level, depending on the scientific problem under consideration. Once a model is developed for a particular problem, it remains to link the model to experimental data. As complex neuronal models often lead to analytically unfeasible likelihood functions, parameter inference can not be achieved by classical maximum-likelihood estimations. To deal with the situation of unknown likelihood functions but take at the same time different sources of uncertainty into account, one framework for parameter inference is Approximate Bayesian Computation (ABC), which is used in various scientific fields (Sisson et al., 2018). Thereby the model is considered as a 'black-box', which does not allow to access any internal information. ABC estimates the distribution of model parameters which is consistent with the experimental data by iteratively evaluating the model on different parameter sets. In recent years, a modified concept of parameter inference has gained attraction due to its efficiency: Simulation based inference (SBI) makes use of surrogate probability functions (Cranmer et al., 2020) and its potentials are currently explored in neuroscience (Gonçalves et al., 2020).

In this thesis, I will present models for different neuronal processes in the retina and how they can be fitted to experimental data. I will show that the ribbon synapses, a highly specialized synapse in the retina (Moser et al., 2020), is an important element for short term adaptational processes. From this synaptic level, I will move on towards a network level of temporal processing in the retina which is necessary to explain the diverse responses of different cell types. I will show

how abstract models of system identification (SI) can be enhanced by biological plausible components to make them more interpretable and allow for *in silico* experiments which are otherwise not possible.
In a second line of research I will show how processing in the retina is differentially tuned depending on the position in the eye. On the example of UV photoreceptors in zebrafish I will present behavioral, anatomical and functional differences. In addition, I will investigate how single synapses of UV photoreceptors are regionally tuned to process and highlight different features of the incoming signal, using computational modeling.
In a final study, I will unravel color processing at the first retinal stage in zebrafish. We will see how functional processing can be linked to the performed computation and efficient coding principles for color vision (Buchsbaum et al., 1983).
Throughout the presented work we will see how the framework of SBI can be exploited in neuroscience to account for stochastic processes but also to link flexibility in the model to uncertainty in the parameter space.

Background

The Retina

In this section, I will give an overview of different biological aspects of the retina as well as of techniques to record functional activity in the retina. It is not intended to be an extensive review but rather highlights specific topics like ribbon synapses or color vision on which the results of this thesis are based.

General Layout of the Retina

The retina is a thin tissue at the back of the eye in which light is detected, visual input gets processed and the signal is finally send to higher brain areas. Although different animals have different needs to cope with their specific natural environment, the overall structure of the retina is surprisingly well conserved across species (Baden et al., 2020).
The retina consists of multiple stacked neuronal layers, each containing different neuron types (Figure 1). We can divide them broadly into three layers of cell bodies and two processing layers. In the processing layers the dendrites or axons of the corresponding neurons stratify and form synapses and the signal is processed to form multiple parallel output channels to the brain (Masland, 2012).
Photoreceptors (PRs), the light sensors of the eye, are located in the outermost layer. They are divided into rod and cone PRs and detect light in their outer segments. Rod PRs mainly contribute to vision under dim light conditions, whereas different cone types form the basis of color vision by responding differentially to light of different wavelengths (see Section Color Vision). Before the output of the PRs is passed on to the bipolar cells (BCs), the signal is shaped by horizontal cell (HC) feedback in the outer plexiform layer (Chapot et al., 2017b). Already in BCs the signal diverges into multiple parallel channels, which have different properties and code different features of the stimulus (Euler et al., 2014; Franke et al., 2017b; Schreyer et al., 2020). In the second synaptic layer, the inner plexiform layer, the signal is further modulated by amacrine cells (ACs) which give mainly inhibitory feedback to BCs and ganglion cells (GCs) (Diamond, 2017). GCs denote the output neurons of the retina which typically collect information from multiple BCs and ACs and send the processed input via their long axons to different brain areas (Baden et al., 2016; Baden et al., 2018).
As in other sensory systems, we can also find highly specialized synapses in the retina. Both, PRs and BCs express ribbon synapses to transmit the signal by

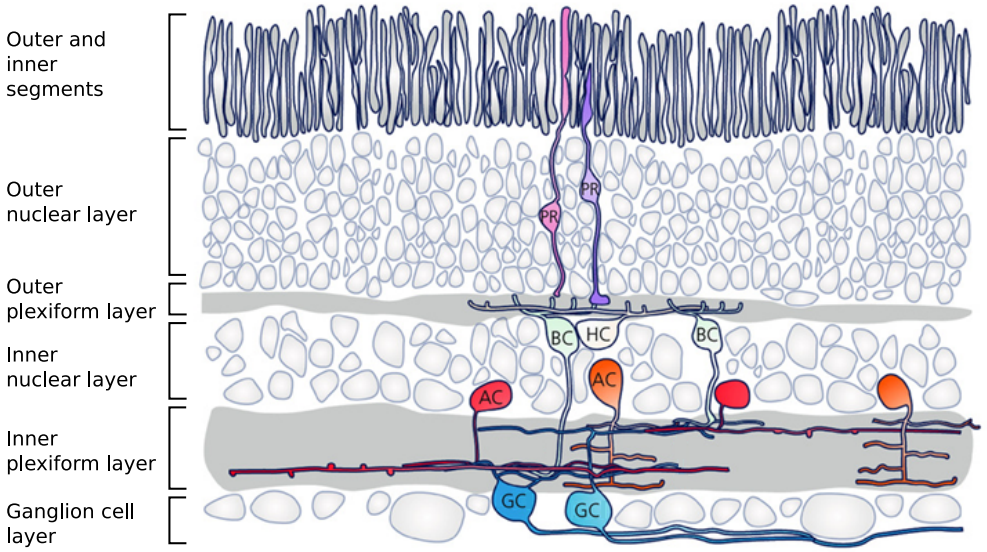

Figure 1: **The Retina.** In the retina light is detected by photoreceptors (PRs) which pass the signal on to bipolar cells (BCs). From here it is further transmitted to ganglion cells (GCs), which project the signal to the brain. In between, the signal is shaped by interneurons in two processing layers: horizontal cells (HCs) operate in the outer and amacrine cells (ACs) in the inner plexiform layer. Figure adapted from Franke et al., 2017a.

releasing glutamate onto the proceeding neuron which enable them to accentuate different coding properties (see Section Ribbon Synapses).

Although the general layout of the retina is similar across species, there exist also a lot of anatomical as well as functional differences. Not only color vision has evolved to different numbers of distinct cone types, but there exist also different complexities in retinal processing. One striking example is the midget pathway in primates, which allows high spatial resolution. Here, PRs in the foveal center of the retina map one-to-one to GCs, which means that only little spatial information is pooled and processed before the signal is send to the brain (Sinha et al., 2017). However, a more common arrangement is found in mice, where each PR contributes to different processing pathways. In mice we find more than 30 parallel output channels which cover the field of view in a mosaic like fashion sending the processed signal to the brain (Baden et al., 2016).

These adaptations are often linked to the efficient coding theory (Barlow et al., 1961). Species have different needs and are exposed to different evolutionary pressure and therefore developed different coding strategies. One additional ecological variable is the varying input statistic. The habitats of different species have varying light statistics, and linking these inputs to computational principles, but also to behavioral consequences, is still an open challenge that has received

substantial attention over the last years (see also Datta et al., 2019 for further discussion).
To understand the underlying principles of vision we therefore need to study different species as model animals, to be able to compare shared mechanisms and identify specific adaptations. While the mouse and also primates are well studied model animals, in recent years (larval) zebrafish gained more attention boosted by the development of new experimental techniques (Baden et al., 2020).

Ribbon Synapses

Ribbon synapses are featured in many sensory systems of vertebrates, such as in auditory hair cells, the vestibular system and especially in the retina (LoGiudice et al., 2009, reviewed in Moser et al., 2020). In the retina they can be found in rod and cone PRs as well as in BCs. They release the excitatory neurotransmitter glutamate onto the subsequent cell. Ribbon synapses are almost exclusively found in early stages in the retina and seem to be especially advantageous for the signaling of early sensory information (Lagnado et al., 2015). They share many fundamental properties with conventional synapses, but can operate in two processing modes: Besides fast transient release of gluatamate they support a continuous mode of release, which is fundamental for the encoding of continuous visual stimuli (Baden et al., 2013a).
In PRs and BCs changes of membrane potential activate presynaptic calcium ion (Ca^{2+}) channels and the increase of intracellular Ca^{2+} concentration drives the glutamate release. The glutamate release is mediated by the ribbon, a protein complex, which acts as a conveyor belt by binding vesicles to active zones and prime them for future release (Sterling et al., 2005; Lagnado et al., 2015). The number of ribbons per synapse varies between species and cell types. While rod terminals in mice only exhibit a single ribbon, cone terminals usually have multiple ribbons (10-50 in mammals), and BCs can have up to hundred such protein complexes (Baden et al., 2013a). Also the anatomical properties of ribbons can vary widely. While rods generally have large ribbons that can dock many hundreds of vesicles at a time, cones usually exhibit multiple smaller ribbons, often positioned at different release sites (Baden et al., 2013a).
The specific molecular and structural tuning of ribbon synapses can enhance different coding properties like low-noise transmission (Hays et al., 2021), temporal precision (James et al., 2019) or high- vs low-amplitude oscillatory behavior (Bellono et al., 2018). But linking this specific molecular and structural tuning to general functional coding rules remains still an open challenge.

Color Vision

The basis of color vision are different types of PRs, which are sensitive to different wavelengths of the electromagnetic spectrum. The eyes of vertebrates developed evolutionarily from a common ancestor, which had four distinct types of cone PRs. These cones differed in their expression of light-sensitive proteins, the opsins. Ancestral cone opsins had their peak sensitivities in the spectrum of UV, blue, green and red light (Baden et al., 2019). The number of cone types in vertebrates varies now across species from one to five. In mice, for example, there exist only two types of cones (sensitive dominantly to short (UV) and mid (green) wavelengths (Szel et al., 1992)), in primates we find three types (blue, green and red), whereas in zebrafish we still find all four 'ancestral' types of cones (reviewed in Meier et al., 2018).
While some key elements like the expressed opsins are conserved across species, a lot of tuning mechanisms developed at different levels of the retina. The structure of PRs in reptiles and birds is for example enhanced by oil droplets which form micro lenses. These lenses sharpen additionally the spectral tuning function of the cones at the cost of a lower overall sensitivity (Baden et al., 2019). Other adaptations are for example different ratios between the cone types (in mice we only find about 5% pure short-wavelength cones (Haverkamp et al., 2005)) or a varying cone type distribution across retinal regions. The best known example is the primate fovea, where no blue cones are located at all (Roorda et al., 1999).
These different adaptations imply different coding strategies for color vision. From a coding perspective, at least two distinct cone types for a discrimination of wavelength and intensity information are needed. By comparing these signals, color opponency is formed which was theoretically studied by Buchsbaum et al. (Buchsbaum et al., 1983). In vertebrates, color opponency is already formed in the outer retina where HCs mediate inhibitory feedback between photoreceptors (Chapot et al., 2017b). The best known opponency motif is the blue-yellow circuit in the primate retina which generalizes to other mammals (Baden et al., 2019). Color opponencies in zebrafish cones is not yet established but will be investigated in Study V for the first retinal stage. However, how these opponent signals are integrated in the upper visual stream is not yet fully understood.

Functional Recordings in the Retina

In neural circuits we can measure the functional activity in terms of at least two proxies: first we can measure the electrical signal which propagates through the neurons, and second, we can measure the concentration of neurotransmitter or second messenger molecules, to quantify the synaptic or intracellular activity.
Historically, functional recordings were first made in single neurons by measuring

the electrical signal via sharp electrodes (Hodgkin et al., 1952; Hubel et al., 1959). This enabled the isolated access to an individual neuron, and with the development of the patch-clamp technique even to single ion channels (Neher et al., 1976). In recent years this technique was expanded to the recording of up to a dozen of neurons simultaneously in brain slice preparations (Wang et al., 2015; Peng et al., 2019). However, these challenging multi-patch experiments which allow the recording of whole neural circuits, are not yet well established for the retina. In the retina the patching technique is currently limited to the recording of single or pairs of cells, but we also see exciting developments for multi-patching experiments (Narayanan, 2018).

Another tool for recording the electric activity in neurons are multi-electrode arrays (MEAs), which enables the recording of spiking activity in whole cell populations. With MEAs, extracellular electrical potentials are recorded by hundreds or thousands of electrodes, which detect signals from all possible sources around (Obien et al., 2015). This could also include different sources of noise, but with advances in nanotechnology new concepts and different layouts are developed which improves the recording quality (Spira et al., 2013; Zeck et al., 2017). For the retina, typically high resolution MEAs with spatial resolution in the range of $10\mu m$ and up to tens of thousands of electrodes are used (Zeck et al., 2017). These setups with recording frequencies of several kHz generate large amounts of data that need to get highly processed before they can be interpreted meaningfully. Particularly, the signals need to be assigned to the individual units (neurons), called 'spike sorting', which is still a non-trivial task in neuroscience (Rey et al., 2015). Importantly, traditional MEAs only allow extracellular recordings which lead to low signal to noise ratios for non-spiking neurons (but see Spira et al., 2013 for further discussion). In the flat mounted retina they favor recordings from the GC layer due to its spatial accessibility but vertical slices allow to access different retinal layers simultaneously (Lee et al., 2020).

The second approach of recording neural activity is to measure the change in concentration of neurotransmitter like glutamate or second messengers like Ca^{2+}. Typically this can be done via optical imaging, by using specialized microscopes. But to record functional activity in the retina via optical imaging, we have to overcome two major drawbacks: first of all, the neural activity has to be made visible and second, we have to avoid a stimulation of the retina - a light-sensitive tissue - by the light induced by the imaging system. Both can be addressed by two-photon imaging, a widely used technique for studying the retina (Euler et al., 2019). The variant of two-photon imaging which was used in the studies presented later works as follow: Fluorescent indicators which change their conformation when binding to a target molecule (e.g. a specific neurotransmitter like glutamate) are delivered to the neural tissue. If they are, in the case of two-photon imaging,

additionally excited by two photons, they emit light of a specific wavelength. The relative change of the recorded fluorescence signal F acts as a proxy for the neural activity, commonly reported as $\Delta F/F$. To avoid the stimulation of the retina by the light used for fluorescence excitation an infrared laser outside the visual spectrum is used (Denk et al., 1990; Denk et al., 1999, see Euler et al., 2019 for a state of the art discussion).
Commonly used fluorescence indicators to record the excitatory activity in the retina are the genetically encoded indicators of the GCaMP family (Chen et al., 2013; Akerboom et al., 2012) or iGluSnFR (Marvin et al., 2013), which target Ca^{2+} and glutamate respectively. Genetically encoded indicators can be introduced into the tissue by a viral approach or permanently expressed in transgenic animal lines. Compared to synthetic indicators which allow 'bulk recordings' of unspecific neuronal populations, genetically encoded indicators can target neuronal subsets selectively (e.g. genetically defined cell types) (Grienberger et al., 2012). Additionally, multiple indicators can be combined to identify specific sub populations or record the concentration of multiple messengers simultaneously (Specht et al., 2017). In addition to the indicators which are targeted at neuromessengers, new and more effective voltage dyes become more and more popular. They change their conformation in response to a change in membrane potential (Chamberland et al., 2017), but as all indicators, they only allow to access relative changes. The temporal precision of the recorded signal is limited by the dynamics of the indicators, which integrate the signal over several hundreds of milliseconds (Chen et al., 2013; Marvin et al., 2013), as well as by technical constraints of the experimental setup (Euler et al., 2019). But with technical advances and under specific experimental conditions high temporal resolutions up to the precision of the timing of single glutamate vesicles can be achieved (James et al., 2019). Besides the temporal resolution, different expression levels of the indicator and various noise sources make the data interpretation additionally challenging (Euler et al., 2019).

These various techniques enable us to record the neuronal signal in all layers of the retina, while having control of the (visual) input to the system. This is not the case for higher brain areas or tasks like memory or decision making and makes the retina, and more generally the visual system, an outstanding model system in neuroscience. The popularity of the visual system is also reflected in a large body of literature on computational models, reaching from retinal models to models of higher visual areas. In the next section I will give a brief overview on different model classes.

Computational Models of the Visual System

Models in computational neuroscience encompass a wide range of details. One extreme denotes detailed models for the diffusion of calcium molecules in single dendrites with exact morphologies (De Schutter et al., 1998; Anwar et al., 2013). The other extreme denotes highly abstracted network models that represent neuron populations as integrate and fire neurons (Brunel et al., 1999, reviewed in Burkitt, 2006) or deep neural network models (DNNs) which are able to model the processing in higher brain areas (Yamins et al., 2014; Cadena et al., 2019). Importantly, there is not a single model explaining all phenomena but the appropriate level of modeling depends on the specific scientific question at hand. Here I want to give a brief overview of different levels of computational models in neuroscience which might be relevant for the retina and the visual system. This is a non-exhaustive list, and is meant to give some examples and to separate into different model categories.

An influential perspective on different model categories was given by D. Marr (Marr, 1982). He grouped models into three levels of abstraction and divided between the hardware implementation, the representation and algorithm, and the computational theory. These levels are all coupled and influence each other, but there is still "a wide choice available at each level" (Marr, 1982).

On the first level, we can place mechanistic, often biophysical Hodgkin-Huxley like models (Hodgkin et al., 1952) in which the different model components are biologically plausible and interpretable. Since they are computationally costly, they are mainly restricted to single cell models (Fohlmeister et al., 1997; Koch, 2004), or models of small networks (Gerstner et al., 2002, see also Guo et al., 2014 for an overview). These models include different ion channels, their dynamics, their density distributions and synaptic processing on various stages of detail. They can be defined deterministically, or incorporate stochasticity at different levels, often in form of channel noise (Goldwyn et al., 2011) or stochastic synaptic release dynamics (Maass et al., 1999). Again the phenomenon under investigation but also the precision of experimental data dictates the nature of the model. For example, data from two-photon imaging often integrates the signal over the time scale of several hundreds of milliseconds, whereas biological plausible channel noise or synaptic release noise act on much smaller time scales. Consequently, they play often a minor role while working with two-photon data.

A well studied mechanism in the retina is for example the photo-transduction cascade in PRs which can be described by a mechanistic model consisting of a system of ordinary differential equations for more than 90 biochemical processes (Invergo et al., 2014). This level of detail is not yet reached for other retinal cell classes, whose physiological properties are not as fully understood and often only

fragmented knowledge across different model species exists. One noteworthy attempt to combine this knowledge across species to inform a multi-compartment Hodgkin-Huxley like model for mouse BCs is Oesterle et al., 2020, where a large body of literature was included to inform priors for simulation based inference (see next section). The study of other retinal cell types and interaction schemes resulted in many pathway specific models. For example, models for local signal processing in horizontal cells (Chapot et al., 2017a), for direction selective circuits (reviewed in Mauss et al., 2017) or for adaptation processes (Jarsky et al., 2011) have been proposed. Nevertheless, already for a pathway specific network level, a detailed explanation including the biochemical processes is missing most of the time and more abstract levels of modeling are chosen (Ölveczky et al., 2007). Constructing a detailed mechanistic model which covers different retinal processing states and reproduces realistic responses to different, also naturalistic stimuli, is still missing and not yet attainable.

Going one level up in Marr's categorization, we can place models of system identification (SI), which aim to maximize the predictive performance and model the input-output relationship (Wu et al., 2006; Freeman et al., 2015; Shah et al., 2019). Such models can come in different flavors, such as statistic Poisson models (Rieke, 1999), including generalizations for large populations (Sokoloski et al., 2020) or the influential model from Pillow et al., 2008, which incorporates feedback terms and linear-non-linear subunits. Furthermore, parallel to the advances in deep learning, there exists an increasing body of work based on DNNs (reviewed in Kriegeskorte, 2015, also McIntosh et al., 2016; Batty et al., 2016; Klindt et al., 2017). These models are often more inspired than constrained by the structure of the neural system which they model, but subunits in the respective models can sometimes be interpreted or linked to subunits of the neural system (Real et al., 2017; Maheswaranathan et al., 2018). Models of SI are able to predict the activity of neurons with remarkable accuracy. They allow us to gain insights into possible algorithmic implementation for different computational tasks but they keep us in the dark about the hardware, i.e. biological implementation. At the same time, drawing conclusions about a representational level is not straightforward and we need to apply techniques such as representational similarity analysis to compare the biological to the *in silico* representation (Kriegeskorte et al., 2008).
Coming back to the retinal processing stages, models of SI are commonly used for single cell as well as for network models. In contrast to the detailed PR model mentioned above, on the level of SI PR are often expressed as convolutions between potentially biphasic kernels with the input signal (Schnapf et al., 1990; Baden et al., 2014). This is computationally much more efficient and reduces the number of free model parameters considerably, but not all properties, such as adaptational processes, can be covered.

The signal processing in other retinal cells is often summarized in a similar manner by linear and non-linear units, with potential time delays, feedback terms and recurrencies (Batty et al., 2016). While the processing in BCs often remains under-explored (but see Schreyer et al., 2020) the processing in the output stage of the retina, namely the GC signals, has been studied intensely. GC models range from small networks of linear-non-linear subunits with feedback terms (Pillow et al., 2008), over more precise descriptions of different receptive field properties and non-linearities (Shi et al., 2019) to DNNs, which became more and more popular in recent years (Klindt et al., 2017; Lindsey et al., 2019; Tanaka et al., 2019). Other models aim to describe specific retinal processing steps, like contrast adaptation (Baccus et al., 2002; Kastner et al., 2019), color processing (Heath et al., 2020) or motion detection (see also Gollisch et al., 2010).
Finally, there are approaches which try to bridge the gap between models of SI and pure mechanistic models: Ozuysal et al. tried to fuse the two approaches into a hybrid model. They defined a linear-non-linear base model and added a first-order kinetic process (Ozuysal et al., 2012). The kinetic block captures different processes for contrast adaptation, but although it can be linked to subunits of the retinal network, a clear biophysical interpretation is difficult. This highlights the challenges of constructing high performing *and* biophysically interpretable models.

On Marr's third level, the computational theory, the *efficient coding hypothesis* is a guiding principle for the visual system (Attneave, 1954; Barlow et al., 1961). The hypothesis postulates that the visual system is designed to process the visual information most efficiently using its limited capacity. For the retina this translates into the hypothesis of optimal coding strategies under different constraints such as the limited capacity of the optic nerve. Already Attneave and Barlow (Attneave, 1954; Barlow et al., 1961) proposed that optimality depends on the environmental statistics and can be studied in the framework of information theory (Cover, 1999). This dependency on the input statistic caught considerable attention (Simoncelli et al., 2001) and offers for example an explanation for the sparseness of retinal spike-trains (Pitkow et al., 2012) or the spatio-temporal profiles of some GC types (Ocko et al., 2018). An analysis of color processing in the framework of optimal coding highlighted the role of color opponency to decorrelate the otherwise highly correlated color channels (Buchsbaum et al., 1983).
However, the formalization of 'optimal' poses still various questions. Often maximally decorrelated signals are viewed as optimal, but see Pitkow et al., 2012 for an extended discussion. An other approach is to maximize the mutual information between stimuli and responses, or to use the reconstruction error of some optimal decoder as a loss function (Gjorgjieva et al., 2014; Ocko et al., 2018; Gjorgjieva et al., 2019). But it has been shown that different loss functions as well as differ-

ent assumptions on noise sources in the neural system can lead to different optima for the neural processing (Brinkman et al., 2016; Gjorgjieva et al., 2019). While the efficient coding hypothesis still sparks research ideas, a cautious look must therefore be taken on the exact formalization of the problem.

The three levels of Marr's categorization give us a rough map to orient in the vast and diverse landscape of computational models. But once the desired model has been constructed, the next step is to link the model to experimental data. Parameter inference is therefore a crucial, but often neglected topic in computational neuroscience and thus I will give a short overview in the next section.

Parameter Inference

Parameter inference is the process of determining parameters such that the predefined model is most coherent with the experimental data. There exist many different concepts on how to perform parameter inference depending on the model framework and model complexity. In this section, I will first present more traditional concepts of parameter inference in neuroscience before outlining recent developments in simulation based inference (SBI) methods which were exploited in Study I, Study IV and Study V.

Common approaches for parameter inference focus on point estimations for one or multiple parameter sets for best performing models. For some statistical models, for example integrate-and-fire models, an analytical likelihood function is available and a closed form solution for the maximum-likelihood estimation can be computed (Paninski et al., 2004). For other models of SI, solutions for differentiable models can be found via gradient descent by taking full advantage of the achievements in deep learning. In Study II I will show, how deep learning frameworks can be used for parameter inference even for models of SI which are enhanced with biologically interpretable components.
For complex mechanistic or non-differentiable models of SI the analytical likelihood function is normally intractable and there is no standard approach to fit these models to data. The used method depends on the model complexity and the loss function. It can range from curve fitting functions (for example implemented in *scipy* (Virtanen et al., 2020)) to evolutionary algorithms (Back, 1996; Fortin et al., 2012) and swarm methods (Vaz et al., 2007), which are better suited for high dimensional parameter spaces and potentially non-convex loss problems.
While these methods are well suited to identify best performing parameters, they do often not allow to draw conclusions about the inferred parameters directly. For this purpose, it is important to take the uncertainty of the inferred parameters into account and investigate the spread of potentially good performing parame-

ters. Although this can be investigated post-hoc via different approaches of *local* sensitivity analysis (Gutenkunst et al., 2007), most methods are based on higher derivatives and do not take the *global* parameter landscape into account.

In contrast, simulation based inference (SBI) tries to infer the posterior distribution of the model parameters Θ on a global scale. As the likelihood function $p(x|\Theta)$ of the model of interest is intractable, it is also called 'likelihood-free' inference. Within this framework, the model is defined via a simulator which can be evaluated for different parameters, but is otherwise inaccessible. More precisely, we can generate samples $x_i \sim p(x|\Theta_i)$, for parameters Θ_i, but we can not evaluate the likelihood function $p(x|\Theta)$.
In recent years, SBI approaches gained more and more attention and the need for efficient methods is increasing in various scientific disciplines which rely on sophisticated computer simulations (reviewed in Cranmer et al., 2020, also Durkan et al., 2018). Following the classification in Cranmer et al., 2020, we can roughly separate into four different types of inference methods:

(i) The first and most established class is the Approximate Bayesian Computation (ABC) framework (Sisson et al., 2018). We can illustrate the concept with the most basic approach of rejection sampling: To infer the posterior distribution $p(\Theta|x_0)$ for the observed data x_0, we draw first parameters Θ_i from a prior. The parameters for which the simulation $x_i \sim p(x|\Theta_i)$ lies within a distance $\varepsilon \geq 0$ from the observed data x_0 (for some distance measure) are accepted and otherwise rejected. Although there exist a lot of more sophisticated methods, including learning an approximation of the intractable likelihood function (Drovandi et al., 2018) and combinations with Markov Chain Monte Carlo (MCMC) methods (Robert et al., 2013), the approximation is only valid in the limit $\varepsilon \to 0$ which makes it prohibitively expensive for computational demanding models. Additionally, we need in general to rerun the inference method for every datapoint x_0 which is not an efficient handling of the computationally expensive simulation results.

In contrast, more recent approaches learn a surrogate model of the parameter-simulation dependency. Once trained, the surrogate model can be evaluated for multiple datapoints x_0. These methods are therefore called amortized methods and fall into the remaining three classes, depending on the surrogate model they infer:

(ii) Likelihood estimation algorithms learn a surrogate model for the intractable likelihood. While early approaches focused on parametric (Gaussian) approaches (Wood, 2010) recent versions use DNNs to approximate the density over x (Lueckmann et al., 2019; Papamakarios et al., 2019b). In a second

step samples from the posterior are drawn via MCMC sampling which adds additional computational overhead.

(iii) Posterior estimation methods learn directly the posterior. Recent methods estimate the density over the parameters Θ via DNNs (Papamakarios et al., 2016; Lueckmann et al., 2017; Greenberg et al., 2019).

(iv) Ratio estimation methods focus on the estimation of the likelihood ratio function $p(x|\Theta_i)/p(x|\Theta_j)$ (Cranmer et al., 2015) or $p(x|\Theta_i)/p(x)$ (Hermans et al., 2020) which is sufficient to draw samples from the posterior via an additional step of MCMC afterwards. One key advantage of this method is that we can formulate it as a *supervised* classification problem in which a DNN is trained to discriminate between two different sets of data. The classifier can then be converted into the likelihood by applying the Neyman–Pearson lemma, also called the likelihood-ratio trick (see also Cranmer et al., 2020 for more references).

For the latter three classes there exist different algorithms which infer the posterior either in one single round or which are sequentially updating a 'proposal prior' distribution. While updating the proposal prior sequentially can lead to more sample efficiency, it can defeat the above mentioned amortization effect by utilizing a specific datapoint x_0 before evaluating the final posterior.

All SBI methods have in common that the approximation usually happens on multiple levels: First, high dimensional data x need to be compressed to a low dimensional feature space, called the summary statistics, which are model and problem dependent. Constructing meaningful, ideally sufficient, summary statistics is already the first obstacle and is highly influencing all further approximations downstream. Often ad-hoc summary statistics are constructed with the help of domain specific knowledge, but new methods for automated construction of summary statistics are developed (Fearnhead et al., 2012; Jiang et al., 2017; Greenberg et al., 2019; Chen et al., 2020).
The next approximation happens in the actual estimation step. While ratio estimation methods use discriminator networks to approximate an ideal discriminator, posterior and likelihood estimation methods highly rely on efficient density inference methods. Common approaches were mixture of Gaussian models (Lueckmann et al., 2017) or kernel density estimations (Gutmann et al., 2016). But with the development of normalizing flows (Papamakarios et al., 2017; Durkan et al., 2019) a much more flexible approach is available which is appealing through its mathematical elegance (reviewed in Papamakarios et al., 2019a).
For the likelihood as well as for the ratio estimation methods an additional approximation of the posterior is performed via MCMC sampling. Recent work

highlights that this step must be carried out carefully, otherwise these powerful methods may be harmed (Lueckmann et al., 2021).
A last approximation happens in presence of limited computational resources. For all methods increasing numbers of model evaluations normally improve the inference quality. As this is a minor problem for fast simulators for which millions of simulations can be run, data efficiency is crucial for computational costly simulators.
This leads to the research direction of active learning. For a more efficient use of the computational resources, several strategies to sample actively new parameters in an informative way have been proposed (Gutmann et al., 2016; Lueckmann et al., 2019; Järvenpää et al., 2019). Active sampling can reduce the needed model evaluations drastically but is adding a computational overhead as well as another approximation stage. Another promising direction for more efficient algorithms is to take apart the simulator and gain access to additional information on latent variables (Brehmer et al., 2020b). Different possibilities for these 'grey-box' models were discussed in Cranmer et al., 2020, and often use advances in machine learning, like probabilistic programming or automatic differentiation.

Overall SBI is a very active field of research and new ideas and algorithms are published continuously (Cranmer et al., 2020). But especially in the absence of the true posterior distribution $p(\Theta|x_0)$ or the true model parameter Θ_0 it is challenging to compare different SBI methods. A first attempt to systematically benchmark SBI methods highlighted that different evaluation metrics compete with each other and do not always provide coherent results (but see Lueckmann et al., 2021 for further discussion). This study, as well as a detailed discussion on recent developments in SBI (Cranmer et al., 2020), suggest that there is not a single method outperforming all others, but the method needs to be chosen based on the problem and the model at hand.
An important step to promote the usage of SBI is to provide open-source toolboxes which can be used by the whole scientific community (Klinger et al., 2018; Gonçalves et al., 2020; Tejero-Cantero et al., 2020). The application of SBI methods to different scientific questions will bring up new challenges and hopefully lead to further cross-pollination between different scientific fields.

Results

In the subsequent chapter I will present the different projects which are included in this dissertation. I will give a motivation and summarize and discuss the main results for each project. The full papers can be found in the Appendix. I will start with two studies on bipolar cell modeling which are bridging the gap between models of system identification and mechanistic models (Study I and Study II). Next I will show how processing in the retina can depend on the retinal region, exemplified by UV cones in zebrafish. First, we will look into behavioral, anatomical and functional differences between regions (Study III) before we zoom in more specifically to the level of single synapses (Study IV). In the last part, we will move to the network level of early retinal color processing – now involving all cone types – in zebrafish retina (Study V).

Study I: Approximate Bayesian Inference for a Mechanistic Model of Vesicle Release at a Ribbon Synapse

Published as: Schröder, James et al. (2019) In: *Advances in Neural Information Processing Systems*. Vol. 32. pp. 7070–7080

Motivation

Ribbon synapses can be found in different cells of the sensory system and their computational advantageous are not yet fully understood. In a recent publication, activity at ribbon synapses of bipolar cells in zebrafish larva was recorded *in vivo* with the resolution of single glutamate vesicles (James et al., 2019). The authors identified multivesicular release events, which are events with multiple glutamate vesicles released simultaneously. They showed that multivesicular release events increased the dynamic range and temporal precision of the signal, and are advantageous for the efficiency of information transmission at the synapse.
To model this complex behavior of ribbon synapses, a model that goes beyond continuous modeling of vesicle movement is necessary to account for the discrete nature of the code. At the same time, synaptic release is a stochastic process and including this variability into an adequate model makes parameter inference challenging as the likelihood function becomes intractable.

Results

We presented a stochastic model of glutamate release at a ribbon synapse in bipolar cells of zebrafish. The model included a linear-non-linear processing stage, followed by a synaptic release compartment which modeled multiple discrete vesicle pools in a biophysically interpretable fashion.

We fitted the linear-non-linear-release model to two-photon microscopy data with single vesicle resolution by using a parametric SBI method. The developed inference method was inspired by Lueckmann et al., 2017, but we inferred the posterior distributions by applying explicit Bayesian updating rules to parametric prior distributions. First, we tested the method on synthetic data and showed that it is able to approximately recover the true parameters, and, at the same time, results in meaningful variances for the posterior. Next, we applied the inference method to experimental data and were able to infer parameter regions for which the variance of the data generated by the model were in the same range as the inter trial variability of the experimental data. Additionally, the model captured the data in terms of release event types, but also extrapolated very well to properties such as temporal precision that were not explicitly optimized for. The model clearly outperformed a generalized linear model, which could not capture the multivesicular release events in an adequate way.

Discussion

The presented model continues the work on hybrid models like linear-non-linear models with a kinetic block presented in Ozuysal et al., 2012, but accounts explicitly for the biophysical structure and processing at the ribbon synapse. The different model parameters are therefore biologically interpretable. In Study II we will see how a deterministic version of the model will serve to make predictions across different cell types. The SBI approach for parameter inference allowed us to derive the model parameters from functional two-photon imaging without highly specialized experiments, which are otherwise often needed to determine individual parameters.

The developed SBI method falls into class (i) of 'traditional' ABC methods, where no surrogate model is trained but the observed data is used directly to infer a posterior distribution. This approach is less flexible compared to recent developments (Cranmer et al., 2020), but as highlighted in Lueckmann et al., 2021 choosing an adequate method is problem specific and traditional ABC algorithms can still outperform more recent approaches, especially for fast model evaluations as in our case.

The presented combination of biophysically inspired mechanistic models with SBI methods allows the development of more interpretable models where no closed-form likelihood is necessary. We showed that taking biophysical constraints into account can even improve prediction accuracy compared to standard models of SI, while being able to link different model components to specific biological structures. The presented model and the developed ideas allowed us to investigate the more complex system of a whole bipolar cell network in the following study.

Study II: System Identification with Biophysical Constraints: A Circuit Model of the Inner Retina

Published as: Schröder, Klindt et al. (2020) In: *Advances in Neural Information Processing Systems*. Vol. 33. pp. 15439–15450

Motivation

In the mouse retina, 14 bipolar cell types exist with functionally diverse stimulus responses (Franke et al., 2017b). Previous work has shown that standard linear-non-linear models can not adequately cover the temporal response properties of all BC types and miss temporal adaptation processes or complex feedback structures (Zhao et al., 2020). These feedback structures arise from more than 60 different amacrine cell types, which is numerically the largest class of cell types in the mouse retina. A complete understanding of their functional processing is still lacking and only some fundamental principles, like the separation in locally and globally processing ACs, and some specific properties, like direction selectivity, have been studied in detail (Masland, 2001; Diamond, 2017).
The challenge was to build a computational model of temporal processing in BCs which is able to reproduce the functional fingerprints of all 14 BC types and at the same time models the structure of the complex AC network as good as possible.

Results

Our model was highly inspired by Euler et al., 2014, which summarizes different processing blocks for BCs. We built a bipolar cell network (BCN) model of temporal processing in the inner retina, which consists of two main parts: (i) the vertical pathway with 14 parallel channels, each a deterministic version of the linear-non-linear-release model from Study I; (ii) the AC network, modeled by a local and global feedback structure, accounting for the different receptive field sizes of AC types (see Appendix B for a schema). We implemented the model in a fully differentiable manner in *pytorch*. We then trained it end-to-end via gradient descent on BC responses to a local and global 'chirp' stimulus (Franke et al., 2017b). The model bridges the gap between pure black-box models of SI and detailed biophysical models: while still biophysically interpretable, the BCN performs on par with or slightly better than a state of the art long short-term memory (LSTM) model. Importantly, it generalizes well to different test datasets of sinusoidal modulations as well as naturalistic stimuli.
As a next step, we compared the learned connectivity weights to a biological connectome of the inner retina, extracted from published electron microscopy data (Helmstaedter et al., 2013) and found striking similarities. Additionally, our model was able to reproduce *in silico* pharmacological experiments by blocking specific pathways or feedback structures, suggesting that it had learned key circuit

functions. As a final step our model predicted biophysical properties of the ribbon synapses, suggesting that these differences could play a key role in the emergence of different BC types.

Discussion

In this work we linked a SI approach with mechanistic components on a circuit level. The model has a high predictive performance while still being biological interpretable. In particular, it enabled us to make predictions on the structure of the biological system, using only information from functional recordings. These predictions can be tested experimentally, which is not possible with standard black-box models of SI.
Comparing the learned connectivity structure to experimental data showed that the model picked up some key functional circuits like cross-over inhibition. Importantly, this work focused on the temporal processing in the inner retina and did not include any spatial components or processing across light levels, although different types of ACs and microcircuits are activated across different stimulus conditions (Diamond, 2017). Including data from more diverse stimulus conditions will be essential for the further understanding of the connectivity structure of retinal neurons, how it follows computational demands and links to optimal coding strategies (see also Discussion).
While the implementation of the model in a fully differentiable manner allowed us to train it with deep learning tools, we only got point estimates for the model parameters. We bypassed this drawback by an ensemble of models with different initializations, resulting in different sets of optimal parameter values. This procedure does not fully account for compensation mechanisms or uncertainty estimations of the parameters. Therefore, applying a SBI method yielding in full posterior approximations would have been desirable, but was not yet feasible for a model with thousands of parameters.

Study III: Fovea-like Photoreceptor Specializations Underlie Single UV Cone Driven Prey-Capture Behavior in Zebrafish

Published as: Yoshimatsu et al. (2020) In: *Neuron*.

Motivation

Many vertebrates have an anatomically and functionally specialized area within the retina, the so called *area temporalis* or *area centralis*. In some species, such as many primates or birds of prey, these specialized regions have further developed into a fovea, where sharp vision with high resolution is possible. These regions can differ from the peripheral regions of the retina in many aspects: A higher cone density, specific pathways (like the midget pathway in primates), or different

receptive field and AC sizes are only some of these specializations (Baden et al., 2020). Another, in most species not previously investigated regional difference could be tuning of PRs. We assumed that within the retina the properties of a single photoreceptor type is matched to a specific set of visual tasks. To test this hypothesis, we studied the differences of UV cone photoreceptors of larval zebrafish across different retinal regions.

Results

We showed that UV cones in the *area temporalis* ('acute zone', AZ) of larval zebrafish are specialized on multiple levels and that prey capture highly relies on these signals. First, we conducted behavioral experiments and demonstrated that larval zebrafish can hardly capture prey in the absence of UV light or if the UV cones were ablated genetically. Confocal microscopy images showed enlarged outer segments of the UV cones in the AZ as well as a higher cone density. This both facilitates photon detection. Next, we used *in vivo* two-photon imaging to show that these cones use an elevated calcium baseline to detect bright objects such as prey. Subsequent transciptomical analysis revealed that this is caused by region-specific tuning of phototransduction genes. We summarized these findings in a computational model for stimulus detection, which showed strong light detection biases in the AZ, but only little differences for the detection of dark events across retinal regions. The functional recordings further revealed that both recovery kinetics of the intracellular calcium as well as response amplitudes were modulated by horizontal cells in the AZ, but not within the other retinal regions. The regional differences in the pre-synaptic calcium signal were later accentuated at the post-synaptic glutamate output, yielding higher information transmission rates at AZ synapses. This set of regionally fine-tuned neural mechanisms facilitates the signaling of UV bright spots within the AZ; indicating that the AZ is optimized for the visual task of prey capture.

Discussion

We showed that UV cones in zebrafish larva express regional specializations in anatomy and function, and that these specializations can be linked to behavioral relevant visual tasks. These specializations support high-resolution UV vision in the AZ, the region that guides prey capturing. Some of the findings, like elongated outer segments of the UV cones in the AZ, were in line with previous findings in other species, like elongated primate foveal cones; however the light-biased AZ in zebrafish contrasts dark biased ventral short-wavelength processing in mice (Baden et al., 2013b). This highlights that anatomical and functional specialization can happen on different neuronal levels, can come in distinct forms across species and is potentially guided by different behavioral tasks.

A preview of our study highlighted the "integrative" approach by covering all three of Marr's principles (Westö et al., 2020). Nevertheless, there are still open research questions: The data suggested an additional tuning of the UV cones on a synaptic level, which we investigated in detail in the next study (Study IV). In the presented work we focused on the signal processing in UV cones, but how zebrafish integrate the input of all four cone types to eventually form color vision is unclear. We will unravel this processing for the first retinal stage in Study V.

Study IV: Distinct Synaptic Transfer Functions in Same-Type Photoreceptors

Published as: Schröder et al. (2021) In: *Elife*.

Motivation

Just like BCs, PRs also feature ribbon synapses to transmit the detected signal to the next processing stage. In the preceding work (Study III), we studied UV cone PRs and found anatomical differences in the outer segments, functional differences in the calcium signal, but also differences in the post-synaptic glutamate signal across different retinal regions. As discussed in Study II, different temporal adaptation processes are potentially implemented *across* different BC types via specific properties of the ribbon synapse. Together with the observed regional differences in the post-synaptic glutamate signal, this raises the questions if and how the synapses *within* one single cone type are differentially tuned across retinal regions to facilitate the encoding of specific visual features.

Results

We first looked into anatomical differences across retinal regions of ribbon synapses of UV cone PRs of larval zebrafish using electron microscopy. We found not only different ribbon sizes, but also striking differences in vesicle densities, suggesting different response properties. Next we employed *in vivo* dual-color two-photon imaging and recorded simultaneously pre-synaptic calcium and post-synaptic glutamate signals. The recorded data showed differences across the different zones in terms of dynamics as well as in response amplitudes. To explore the computational implementation of the processing differences, we constructed a model of a ribbon synapse based on previous work (Baden et al., 2014). The model was built using relative occupancies of different vesicle pools and consists of a set of coupled ordinary differential equations. We inferred the parameters for each retinal region via a SBI method (Lueckmann et al., 2017) which yielded approximated posterior distributions. This gave us the possibility to compare parameter distributions across retinal regions. We found different calcium-to-glutamate transfer functions depending on the location in the eye. Additionally, this al-

lowed us to conduct a sensitivity analysis to investigate the influence of the different model parameters on the model output. The analysis showed, that different properties of the ribbon synapse are highly influencing the response properties at different time points. As a final step, we applied the model on new stimuli and studied the encoding properties of different ribbon configurations. We found that the calcium baseline played a major role, for example in setting an On versus Off processing bias, but even with a fixed calcium baseline the ribbon could be fine-tuned to facilitate different coding properties. We provided the model as an online tool to facilitate further exploration, allowing the user to control all key parameters. Overall, we showed that already on the synaptic level of single neuron types highly specialized mechanisms can occur which favor the encoding of different visual features.

Discussion

This study complements and extends the findings of Study III by identifying regional differences on the synaptic level of UV cones. The presented model showed parameter dependent coding properties and highlighted the importance of calcium handling at ribbon synapses. This is in line with recent findings from Özçete et al., 2020 in the mouse auditory system, in which ribbon synapses also occur. More specifically, they found heterogeneous voltage dependency of Ca^{2+} channels and heterogeneous Ca^{2+} release dynamics even within *individual* inner hair cells (Özçete et al., 2020). They argue that this could be advantageous to diversify the dynamic range for intensity coding in upstream cells. Although they focused on calcium processing in the synapse, the authors conclude, similar to us, that single neurons and their synapses in the sensory system are tuned to transmit specific features of the incoming signal.

The use of SBI allowed us an in-depth investigation of the model parameters, a comparison across different retinal regions, and to link the parameters directly to biological properties. Furthermore, in combination with sensitivity analysis we passed the uncertainty in the parameter space on to the parameter-dependent expected variance of the model output. This nicely displayed the time-dependent influence of different model parameters on the model output and highlighted the interplay of different biological properties to tune the system to encode specific features.

Study V: Ancestral Circuits for Vertebrate Color Vision Emerge at the First Retinal Synapse

Published as: Yoshimatsu et al. (2021) In: *Science Advances*.

Motivation

Encoding the color of an object can add behavioral relevant information to the perceived scene. But as the spectrum of natural light is highly correlated, it is necessary to compare signals of at least two distinct cone types to separate intensity from wavelength information. For example, zebrafish possess all four 'ancestral' cone types (red, green, blue and UV) and three HC types which already shape the visual signal at the very first synapse of the visual pathway. While there is some knowledge on color processing in mice or primates, little is known about the functional and anatomical circuit principles in zebrafish and other tetrachromatic species.
The goal of this study was to identify the color tuning of the different cone types in zebrafish larva, how these tuning links to the light statistics of their natural environment and how the computation is implemented on a circuit level.

Results

We recorded *in vivo* cone activity with two-photon imaging in the pre-synaptic terminals, i.e. the output of the PRs. In the experiments we stimulated the retina with LEDs of different wavelengths, which covered the whole activation spectrum of cone opsins. Based on the recordings we extracted tuning functions of the different cone types. We found that red and UV cones matched their opsin tuning profiles, whereas green and blue cones' tuning functions were biphasic with a color opponency in high- and mid- wavelength domains respectively. To investigate the origin of these opponencies, we identified the anatomical connectivity of cones and HCs in the outer retina via EM and confocal imaging. This connectivity was then used to inform the possible connectivity in a linear circuit model, which identified HCs of type one to underlie most spectral tuning. The parameters of the model were inferred via SBI, estimating the connectivity matrix of cone to HC connections including uncertainties. We verified the model by two-photon voltage imaging of HC somata, and the tuning curves of the HCs matched the model predictions surprisingly well. This indicated that our model did not only reproduce the output but also captured the neural processing in the system.
To link the functional tuning of the cones to natural statistics, we next performed principal component analysis (PCA) on hyperspectral images of natural scenes and identified the axes that optimally captured the variance of the images. We found that the first principal component covered achromatic information, and the second and third components formed the major chromatic axes. Surprisingly, the

tuning curves of the red and green cones almost perfectly matched the first and second principle components. Additionally, blue cones were tuned to capture most remaining variance when opposed to green cones, which could potentially be implemented in the upper visual stream. UV cones however represented an 'UV-private' axis, which did not interfere with the other channels. We performed the same analysis on published data of photoreceptor tuning curves from fruit flies and found essentially the same strategy: to extract spectral information, the encoding space was rotated by the fruit flies' PRs to the major axes of the PCA.
Overall, we established the complete architecture of color processing in the outer retina of larval zebrafish. We showed that rotating color space into achromatic and chromatic axes at the first synapse of the visual system may be a fundamental principle of color vision across species.

Discussion

In this study we presented a full description of color processing at the first synapse of the larval zebrafish's visual system. We covered all three of Marr's levels by deconstructing the anatomical implementation by EM analysis, the representational level by functional recordings and modeling, and the computational level by linking the results to natural scene statistics.
Surprisingly, we found an efficient decomposition of the visual signal into intensity and color channels already at the first synapse of the system. While our study is partly in line with theoretical work on optimal color processing (Buchsbaum et al., 1983), it raises questions on the definition of 'optimality'. While PCA prioritizes on features and contrasts that are most common in the signal, it remains unclear if this is the optimal strategy: some rare events could be highly relevant for survival. The identified 'UV-private' channel, which potentially facilitates prey capture (see Study III), hints that the definition of 'optimal' is more complex, but a general theoretical framework which takes behavioral relevance into account is still missing.
Additionally, it is not yet fully understood how the color signal is further processed in later stages of the visual system. While our study focused on the spectral decomposition of the color signal we did not include any temporal or spatial analysis, but a composition of these features form the neural code in later stages (Zhou et al., 2020). Disentangling these complex neural signals and linking them to naturalistic stimuli is an interesting and challenging research direction which will lead to a more comprehensive understanding of how the brain processes color information.

Discussion

In this work I presented different approaches for modeling retinal activity and how model parameters can be inferred from experimental data. Additionally, I investigated tuning properties of photoreceptors across different retinal regions and color processing at the first retinal stage in larval zebrafish. Throughout the presented studies, I attempted to link the three levels of Marr (Marr, 1982): biological implementation, functional properties and performed computations.

In Study I and Study II we designed two models of system identification (SI) which are constrained by biologically plausible structures. The presented models do not only outperform standard black-box models of SI for the specific tasks, but they also allow us to draw conclusions about the implementation in the biological system. More specifically, we identified the ribbon synapse as a key feature for short-term adaptation processes in the inner retina. Additionally, we were able to show that the connectivity between BCs and ACs follow computational needs for temporal processing. However, this is but the first step to more interpretable models of SI of the retina. A first extension of this hybrid model approach to temporal processing in the GC layer did highlight the necessity of adequate data to constrain the model meaningfully (Klindt et al., 2021). It is obvious, that features like direction or orientation selectivity cannot be studied by pure temporal stimuli. Additionally, different microcircuits including different ACs can be activated under different stimulus conditions (Chen et al., 2016). Therefore, especially diverse spatio-temporal stimuli will be important to study spatial integration across cell types. Another way to get more adequate data to study signal processing between different cell classes is to access functional activity across multiple layers of the retina. Recent developments now allow to measure different cell classes simultaneously by 'vertical' x-z scans (Zhao et al., 2020).
Furthermore, multimodal datasets will offer new approaches to analyze neural systems from multiple viewpoints. Patch-seq data (consisting of paired functional recordings, gene expression levels and morphological data (Cadwell et al., 2016)) already led to substantial progress in cell type classification in the cortex (Scala et al., 2020; Gouwens et al., 2020). Integrating different data modalities of the same cell into one model could also help to couple Marr's levels. For the retina, such a dataset could consist of a functionally annotated connectomics dataset, which combines functional two-photon recordings of cell activity across multiple layers with a reconstruction of the connectivity structure via electron microscopy. This could deepen our understanding on how functional properties in the retina arise from its circuit implementations.

The approach of biological constrained models of SI (see also Real et al., 2017) is contrasted by the expanding work on DNNs modeling the retinal processing (McIntosh et al., 2016; Klindt et al., 2017; Maheswaranathan et al., 2018). Although these models offer a prodigious accuracy, even across visual tasks, they often lack biological interpretability and it remains difficult to draw conclusions on the implementational level. However, in a recent work, the authors systematically reduced their retinal DNN model to minimal subnetworks that were still able to generate complex response behaviors. By doing so, they claimed to gain conceptual insights and summarize computational mechanisms (Tanaka et al., 2019). Nevertheless, the insights remained on an abstract level and could not be linked to the network implementation in the retina. Apart from direct comparisons to neural circuits, retinal DNN models can also be used as an analysis tool, for example to refine retinal cell type classification (Höfling et al., 2020).
In conclusion, constraining models of SI by biologically plausible mechanisms is a promising avenue in systems neuroscience. Combining the benefits of modern DNN frameworks with components of mechanistic models may lead to sophisticated models which can still be efficiently trained. These models can give powerful explanations on a biophysical level, allow for testing and generating new hypotheses and may lead to new insights into signal processing in the retina in particular and neural systems in general.

In a second line of research, we investigated regional specializations of photoreceptors and their color processing in larval zebrafish (Study III, Study IV and Study V). We found that UV photoreceptors are regionally tuned on multiple levels and we linked the tuning pattern to the requirements of prey capture behavior. A study conducted in parallel suggested that neural circuits in the mouse retina are also regionally tuned and particularly support color vision in the upper visual field (Szatko et al., 2020). Their findings can potentially be explained by substantial differences of the wavelength statistics between the upper and lower visual field of natural scenes for mice (Qiu et al., 2020). These studies highlight that different species, even without possessing a fovea, express high asymmetries within their retinas, that these asymmetries are species dependent and that they can range from synapses to circuits. Therefore, as highlighted previously (Baden et al., 2020), we need to study multiple model systems and identify common principles to understand the basic concepts of vision.
One challenge is to link the functional level of retinal circuits to the computation they perform. In Study V we could provide this link by showing that color processing at the first synaptic level in zebrafish is optimized to rotate the colorspace in a PCA-like manner. In our work we profited from previously recorded data of natural images (Zimmermann et al., 2018; Nevala et al., 2019) as well as from flexible visual stimuli which allowed to measure neural responses across a broad

spectrum of stimulus wavelengths (Zimmermann et al., 2020). This demonstrates that to elucidate the neural network in the retina, it is of particular importance to design meaningful stimuli for functional recordings. A perfect stimulus would include all relevant features of the natural environment and, at the same time, would be controllable in all essential (e.g. spatial, temporal, chromatic and potentially more unknown) dimensions. However, even then a carefully designed experimental setup remains crucial as even simple effects like refraction or reflection of the stimulus can introduce stimulus artifacts and lead to wrong conclusions (Wang et al., 2021). Recordings with such complex stimuli are also challenging the efficient coding hypothesis as the definition of 'optimal' allows for some flexibility as discussed in Section Computational Models of the Visual System (see also discussion in Study V). Additionally, linking the complex stimulus space to behavioral tasks would introduce many unknowns which makes a mathematically rigorous derivation of optimal configurations, like for the On and Off pathway splitting in sensory systems (Gjorgjieva et al., 2014), demanding.

In Study I, Study IV and Study V we showcased the potentials of applying simulation based inference (SBI) in system neuroscience. At the same time another study demonstrated that SBI can be successfully applied to detailed mechanistic models by carefully selecting appropriate priors and iteratively constraining the parameter space (Oesterle et al., 2020).
It is long known that similar neural model output and especially simulated network activity can arise from very different model parameters (Prinz et al., 2004; Marder et al., 2011). It is important to acknowledge that this ambiguity is not a failure of the model, but inherent to neural systems. For example, there exists a high variability in ion channel properties which can lead to reliable and similar response behaviors of neurons (reviewed in Goaillard et al., 2021). This robustness mechanism complicates solving the inverse problem of parameter inference: Any simple assignment of single best performing parameters might ignore the complexity of the biological system. In the context of biophysical models, covariates like temperature add further complexity by altering relative contributions of ion currents or other latent variables, but may explain biological benefits of compensatory mechanisms (Alonso et al., 2020). An analysis of the full posterior estimations, which can be obtained via SBI, can help to explain these compensatory mechanisms and lead to new hypotheses like the role of energy consumption for similarly behaving neurons (Deistler et al., 2021). Adding SBI to the diverse toolbox of computational neuroscience can therefore lead to a better understanding of model uncertainty and its link to biological variability.
Consequently, neuroscience can profit from achievements in the vibrant field of machine learning and apply new developments made in this field. However, for models with more than dozens of parameters, scalability remains a major obstacle.

Although normalizing flows (reviewed in Papamakarios et al., 2019a) represent a powerful concept to approximate arbitrary probability distributions, the curse of dimensionality still prevents an efficient estimation of high dimensional distributions. A possible way of dimensionality reduction could be achieved by learning potential manifolds in the parameter space. Simultaneously learning a probability distribution on these manifolds (Brehmer et al., 2020a) could even lead to more efficient techniques to investigate parameter dependencies .
As demonstrated in Study IV, SBI additionally allows to perform sensitivity analysis on a global scale of the parameter space. While classical gradient methods for parameter optimization are restricted to local estimations based on higher derivatives (Gutenkunst et al., 2007), SBI enables a global analysis by using the inferred posterior distributions for a varianced based sensitivity analysis (Saltelli et al., 2008; Glen et al., 2012; Tennøe et al., 2018). Although this is a promising way to measure the global model sensitivity, it results in a complex interplay between the approximated posterior and the parameter influence on the model output. Disentangling this interplay is a direction of further research.
Having highlighted the potentials of SBI, one of its pitfalls lies in model comparison and model misspecification. Common criteria for model comparison, like Bayes' factor, fail theoretically in the SBI setting (Robert et al., 2011) or are empirically of poor quality (Marin et al., 2018). Different sampling approaches for model selection have been proposed (Toni et al., 2010; Marin et al., 2018), including additional training of random forest trees (Pudlo et al., 2016), which all come with the burden of high computational costs and can be of low fidelity for ill chosen sets of summary statistics (Marin et al., 2018).
In the context of model misspecification in Bayesian inference, current results are mainly limited to simple linear models. Already in the setting of exact Bayesian computation 'worse' models might be preferred over 'better' ones if no correction mechanisms are considered (Grünwald et al., 2017). The approximate computation setting reveals similar difficulties, but each level of approximation (see Section Parameter Inference) may influence the results differently and general conclusions are difficult to draw (Frazier et al., 2020; Frazier et al., 2021). Thus, a well specified model which is able to replicate experimental recordings is essential for trustworthy SBI, but identifying such models remains difficult. These unsatisfactory intermediate results highlight the necessity for further research in the direction of model comparison and misspecification in the SBI setting, especially as it is becoming a more widely used tool in neuroscience and other scientific fields.

This thesis demonstrates how recent developments in machine learning can be successfully applied in computational neuroscience. We have seen how these developments can help to couple the three levels of Marr by allowing new types

of biophysical constrained models as well as efficient inference methods. Further progress in experimental techniques will increase the need for appropriate machine learning and modeling tools to be able to cope with larger and more complex data. A strong interaction between machine learning and neuroscience will therefore be crucial for the further understanding of neural systems, but can also inspire machine learning researches to make use of computational principles found in these systems.

References

Akerboom, Jasper, Tsai-Wen Chen, Trevor J Wardill, Lin Tian, Jonathan S Marvin, Sevinç Mutlu, Nicole Carreras Calderón, Federico Esposti, Bart G Borghuis, Xiaonan Richard Sun, et al. (2012). "Optimization of a GCaMP calcium indicator for neural activity imaging". *Journal of neuroscience* 32.40, pp. 13819–13840.

Alonso, Leandro M and Eve Marder (2020). "Temperature compensation in a small rhythmic circuit". *Elife* 9, e55470.

Anwar, Haroon, Iain Hepburn, Hermina Nedelescu, Weiliang Chen, and Erik De Schutter (2013). "Stochastic calcium mechanisms cause dendritic calcium spike variability". *Journal of Neuroscience* 33.40, pp. 15848–15867.

Attneave, Fred (1954). "Some informational aspects of visual perception." *Psychological review* 61.3, p. 183.

Baccus, Stephen A and Markus Meister (2002). "Fast and slow contrast adaptation in retinal circuitry". *Neuron* 36.5, pp. 909–919.

Back, Thomas (1996). *Evolutionary algorithms in theory and practice: evolution strategies, evolutionary programming, genetic algorithms*. Oxford university press.

Baden, Tom, Philipp Berens, Katrin Franke, Miroslav Román Rosón, Matthias Bethge, and Thomas Euler (2016). "The functional diversity of retinal ganglion cells in the mouse". *Nature* 529.7586, pp. 345–350.

Baden, Tom, Thomas Euler, and Philipp Berens (2020). "Understanding the retinal basis of vision across species". *Nature Reviews Neuroscience* 21.1, pp. 5–20.

Baden, Tom, Thomas Euler, Matti Weckström, and Leon Lagnado (2013a). "Spikes and ribbon synapses in early vision". *Trends in neurosciences* 36.8, pp. 480–488.

Baden, Tom, Anton Nikolaev, Federico Esposti, Elena Dreosti, Benjamin Odermatt, and Leon Lagnado (2014). "A synaptic mechanism for temporal filtering of visual signals". *PLoS biology* 12.10.

Baden, Tom and Daniel Osorio (2019). "The retinal basis of vertebrate color vision". *Annual review of vision science* 5, pp. 177–200.

Baden, Tom, Timm Schubert, Philipp Berens, and Thomas Euler (2018). "The functional organization of vertebrate retinal circuits for vision". *Oxford Research Encyclopedia of Neuroscience*.

Baden, Tom, Timm Schubert, Le Chang, Tao Wei, Mariana Zaichuk, Bernd Wissinger, and Thomas Euler (2013b). "A tale of two retinal domains: near-optimal sampling of achromatic contrasts in natural scenes through asymmetric photoreceptor distribution". *Neuron* 80.5, pp. 1206–1217.

Barlow, Horace B et al. (1961). “Possible principles underlying the transformation of sensory messages”. *Sensory communication* 1.01.

Batty, Eleanor, Josh Merel, Nora Brackbill, Alexander Heitman, Alexander Sher, Alan Litke, EJ Chichilnisky, and Liam Paninski (2016). “Multilayer recurrent network models of primate retinal ganglion cell responses”.

Bellono, Nicholas W, Duncan B Leitch, and David Julius (2018). “Molecular tuning of electroreception in sharks and skates”. *Nature* 558.7708, pp. 122–126.

Brehmer, Johann and Kyle Cranmer (2020a). “Flows for simultaneous manifold learning and density estimation”. *arXiv preprint arXiv:2003.13913*.

Brehmer, Johann, Gilles Louppe, Juan Pavez, and Kyle Cranmer (2020b). “Mining gold from implicit models to improve likelihood-free inference”. *Proceedings of the National Academy of Sciences* 117.10, pp. 5242–5249.

Brinkman, Braden AW, Alison I Weber, Fred Rieke, and Eric Shea-Brown (2016). “How do efficient coding strategies depend on origins of noise in neural circuits?” *PLoS computational biology* 12.10, e1005150.

Brunel, Nicolas and Vincent Hakim (1999). “Fast global oscillations in networks of integrate-and-fire neurons with low firing rates”. *Neural computation* 11.7, pp. 1621–1671.

Buchsbaum, Gershon and Allan Gottschalk (1983). “Trichromacy, opponent colours coding and optimum colour information transmission in the retina”. *Proceedings of the Royal society of London. Series B. Biological sciences* 220.1218, pp. 89–113.

Burkitt, Anthony N (2006). “A review of the integrate-and-fire neuron model: I. Homogeneous synaptic input”. *Biological cybernetics* 95.1, pp. 1–19.

Cadena, Santiago A, George H Denfield, Edgar Y Walker, Leon A Gatys, Andreas S Tolias, Matthias Bethge, and Alexander S Ecker (2019). “Deep convolutional models improve predictions of macaque V1 responses to natural images”. *PLoS computational biology* 15.4, e1006897.

Cadwell, Cathryn R, Athanasia Palasantza, Xiaolong Jiang, Philipp Berens, Qiaolin Deng, Marlene Yilmaz, Jacob Reimer, Shan Shen, Matthias Bethge, Kimberley F Tolias, et al. (2016). “Electrophysiological, transcriptomic and morphologic profiling of single neurons using Patch-seq”. *Nature Biotechnology* 34.2, p. 199.

Chamberland, Simon, Helen H Yang, Michael M Pan, Stephen W Evans, Sihui Guan, Mariya Chavarha, Ying Yang, Charleen Salesse, Haodi Wu, Joseph C Wu, et al. (2017). “Fast two-photon imaging of subcellular voltage dynamics in neuronal tissue with genetically encoded indicators”. *Elife* 6, e25690.

Chapot, Camille A, Christian Behrens, Luke E Rogerson, Tom Baden, Sinziana Pop, Philipp Berens, Thomas Euler, and Timm Schubert (2017a). “Local signals in mouse horizontal cell dendrites”. *Current Biology* 27.23, pp. 3603–3615.

Chapot, Camille A, Thomas Euler, and Timm Schubert (2017b). "How do horizontal cells 'talk'to cone photoreceptors? Different levels of complexity at the cone–horizontal cell synapse". *The Journal of physiology* 595.16, pp. 5495–5506.

Chen, Qiang, Zhe Pei, David Koren, and Wei Wei (2016). "Stimulus-dependent recruitment of lateral inhibition underlies retinal direction selectivity". *Elife* 5, e21053.

Chen, Tsai-Wen, Trevor J Wardill, Yi Sun, Stefan R Pulver, Sabine L Renninger, Amy Baohan, Eric R Schreiter, Rex A Kerr, Michael B Orger, Vivek Jayaraman, et al. (2013). "Ultrasensitive fluorescent proteins for imaging neuronal activity". *Nature* 499.7458, pp. 295–300.

Chen, Yanzhi, Dinghuai Zhang, Michael Gutmann, Aaron Courville, and Zhanxing Zhu (2020). "Neural approximate sufficient statistics for implicit models". *arXiv preprint arXiv: 2010.10079*.

Cover, Thomas M (1999). *Elements of information theory*. John Wiley & Sons.

Cranmer, Kyle, Johann Brehmer, and Gilles Louppe (2020). "The frontier of simulation-based inference". *Proceedings of the National Academy of Sciences* 117.48, pp. 30055–30062.

Cranmer, Kyle, Juan Pavez, and Gilles Louppe (2015). "Approximating likelihood ratios with calibrated discriminative classifiers". *arXiv preprint arXiv: 1506.02169*.

Datta, Sandeep Robert, David J Anderson, Kristin Branson, Pietro Perona, and Andrew Leifer (2019). "Computational neuroethology: a call to action". *Neuron* 104.1, pp. 11–24.

De Schutter, Erik and Paul Smolen (1998). "Calcium dynamics in large neuronal models". *Methods in neuronal modeling: From ions to networks* 2.

Deistler, Michael, Pedro Goncalves, and Jakob H Macke (2021). "Disparate energy consumption despite similar network activity". *Cosyne Abstract*.

Denk, Winfried and Peter B Detwiler (1999). "Optical recording of light-evoked calcium signals in the functionally intact retina". *Proceedings of the National Academy of Sciences* 96.12, pp. 7035–7040.

Denk, Winfried, James H Strickler, and Watt W Webb (1990). "Two-photon laser scanning fluorescence microscopy". *Science* 248.4951, pp. 73–76.

Diamond, Jeffrey S (2017). "Inhibitory interneurons in the retina: types, circuitry, and function". *Annual review of vision science* 3, pp. 1–24.

Drovandi, Christopher C, Clara Grazian, Kerrie Mengersen, and Christian Robert (2018). "Approximating the Likelihood in ABC". *Handbook of approximate bayesian computation*, pp. 321–368.

Durkan, Conor, Artur Bekasov, Iain Murray, and George Papamakarios (2019). "Neural spline flows". *Advances in Neural Information Processing Systems*, pp. 7509–7520.

Durkan, Conor, George Papamakarios, and Iain Murray (2018). "Sequential neural methods for likelihood-free inference". *arXiv preprint arXiv:1811.08723*.

Euler, Thomas, Katrin Franke, and Tom Baden (2019). "Studying a light sensor with light: multiphoton imaging in the retina". *Multiphoton Microscopy*. Springer, pp. 225–250.

Euler, Thomas, Silke Haverkamp, Timm Schubert, and Tom Baden (2014). "Retinal bipolar cells: elementary building blocks of vision". *Nature Reviews Neuroscience* 15.8, pp. 507–519.

Fearnhead, Paul and Dennis Prangle (2012). "Constructing summary statistics for approximate Bayesian computation: Semi-automatic approximate Bayesian computation". *Journal of the Royal Statistical Society: Series B (Statistical Methodology)* 74.3, pp. 419–474.

Fohlmeister, JF and RF Miller (1997). "Impulse encoding mechanisms of ganglion cells in the tiger salamander retina". *Journal of neurophysiology* 78.4, pp. 1935–1947.

Fortin, Félix-Antoine, François-Michel De Rainville, Marc-André Gardner Gardner, Marc Parizeau, and Christian Gagné (2012). "DEAP: Evolutionary algorithms made easy". *The Journal of Machine Learning Research* 13.1, pp. 2171–2175.

Franke, Katrin and Tom Baden (2017a). "General features of inhibition in the inner retina". *The Journal of physiology* 595.16, pp. 5507–5515.

Franke, Katrin, Philipp Berens, Timm Schubert, Matthias Bethge, Thomas Euler, and Tom Baden (2017b). "Inhibition decorrelates visual feature representations in the inner retina". *Nature* 542.7642, pp. 439–444.

Frazier, David T, Christopher Drovandi, and David J Nott (2021). "Synthetic Likelihood in Misspecified Models: Consequences and Corrections". *arXiv preprint arXiv: 2104.03436*.

Frazier, David T, Christian P Robert, and Judith Rousseau (2020). "Model misspecification in approximate Bayesian computation: consequences and diagnostics". *Journal of the Royal Statistical Society: Series B (Statistical Methodology)* 82.2, pp. 421–444.

Freeman, Jeremy, Greg D Field, Peter H Li, Martin Greschner, Deborah E Gunning, Keith Mathieson, Alexander Sher, Alan M Litke, Liam Paninski, Eero P Simoncelli, et al. (2015). "Mapping nonlinear receptive field structure in primate retina at single cone resolution". *Elife* 4, e05241.

Gerstner, Wulfram and Werner M Kistler (2002). *Spiking neuron models: Single neurons, populations, plasticity*. Cambridge university press.

Gjorgjieva, Julijana, Markus Meister, and Haim Sompolinsky (2019). "Functional diversity among sensory neurons from efficient coding principles". *PLoS computational biology* 15.11, e1007476.

Gjorgjieva, Julijana, Haim Sompolinsky, and Markus Meister (2014). "Benefits of pathway splitting in sensory coding". *Journal of Neuroscience* 34.36, pp. 12127–12144.

Glen, Graham and Kristin Isaacs (2012). “Estimating Sobol sensitivity indices using correlations”. *Environmental Modelling & Software* 37, pp. 157–166.

Goaillard, Jean-Marc and Eve Marder (2021). “Ion Channel Degeneracy, Variability, and Covariation in Neuron and Circuit Resilience”. *Annual Review of Neuroscience* 44.

Goldwyn, Joshua H and Eric Shea-Brown (2011). “The what and where of adding channel noise to the Hodgkin-Huxley equations”. *PLoS Comput Biol* 7.11, e1002247.

Gollisch, Tim and Markus Meister (2010). “Eye smarter than scientists believed: neural computations in circuits of the retina”. *Neuron* 65.2, pp. 150–164.

Gonçalves, Pedro J, Jan-Matthis Lueckmann, Michael Deistler, Marcel Nonnenmacher, Kaan Öcal, Giacomo Bassetto, Chaitanya Chintaluri, William F Podlaski, Sara A Haddad, Tim P Vogels, et al. (2020). “Training deep neural density estimators to identify mechanistic models of neural dynamics”. *Elife* 9, e56261.

Gouwens, Nathan W, Staci A Sorensen, Fahimeh Baftizadeh, Agata Budzillo, Brian R Lee, Tim Jarsky, Lauren Alfiler, Katherine Baker, Eliza Barkan, Kyla Berry, et al. (2020). “Integrated morphoelectric and transcriptomic classification of cortical GABAergic cells”. *Cell* 183.4, pp. 935–953.

Greenberg, David, Marcel Nonnenmacher, and Jakob H Macke (2019). “Automatic posterior transformation for likelihood-free inference”. *International Conference on Machine Learning*. PMLR, pp. 2404–2414.

Grienberger, Christine and Arthur Konnerth (2012). “Imaging calcium in neurons”. *Neuron* 73.5, pp. 862–885.

Grünwald, Peter and Thijs Van Ommen (2017). “Inconsistency of Bayesian inference for misspecified linear models, and a proposal for repairing it”. *Bayesian Analysis* 12.4, pp. 1069–1103.

Guo, Tianruo, David Tsai, Siwei Bai, John W Morley, Gregg J Suaning, Nigel H Lovell, and Socrates Dokos (2014). “Understanding the retina: A review of computational models of the retina from the single cell to the network level”. *Critical Reviews™ in Biomedical Engineering* 42.5.

Gutenkunst, Ryan N, Joshua J Waterfall, Fergal P Casey, Kevin S Brown, Christopher R Myers, and James P Sethna (2007). “Universally sloppy parameter sensitivities in systems biology models”. *PLoS Comput Biol* 3.10, e189.

Gutmann, Michael U, Jukka Corander, et al. (2016). “Bayesian optimization for likelihood-free inference of simulator-based statistical models”. *Journal of Machine Learning Research*.

Haverkamp, Silke, Heinz Wässle, Jens Duebel, Thomas Kuner, George J Augustine, Guoping Feng, and Thomas Euler (2005). “The primordial, blue-cone color system of the mouse retina”. *Journal of Neuroscience* 25.22, pp. 5438–5445.

Hays, Cassandra L, Greg D Field, and Wallace Thoreson (2021). "Properties of multivesicular release from rod photoreceptors support transmission of single photon responses". *bioRxiv*.

Heath, Sarah L, Matthias P Christenson, Elie Oriol, Maia Saavedra-Weisenhaus, Jessica R Kohn, and Rudy Behnia (2020). "Circuit mechanisms underlying chromatic encoding in Drosophila photoreceptors". *Current Biology* 30.2, pp. 264–275.

Helmstaedter, Moritz, Kevin L Briggman, Srinivas C Turaga, Viren Jain, H Sebastian Seung, and Winfried Denk (2013). "Connectomic reconstruction of the inner plexiform layer in the mouse retina". *Nature* 500.7461, pp. 168–174.

Hermans, Joeri, Volodimir Begy, and Gilles Louppe (2020). "Likelihood-free mcmc with amortized approximate ratio estimators". *International Conference on Machine Learning*. PMLR, pp. 4239–4248.

Hodgkin, Alan L and Andrew F Huxley (1952). "A quantitative description of membrane current and its application to conduction and excitation in nerve". *The Journal of physiology* 117.4, pp. 500–544.

Hubel, David H and Torsten N Wiesel (1959). "Receptive fields of single neurones in the cat's striate cortex". *The Journal of physiology* 148.3, pp. 574–591.

Höfling, Lara, Christian Behrens, Bethge Matthias Szatko Klaudia, Philipp Berens, Katrin Franke, Alexander S Ecker, and Thomas Euler (2020). "Unraveling RGC function through modeling of natural movie responses". *Bernstein Conference 2020*. doi: 10.12751/nncn.bc2020.0088. Accessed 19.4.2021.

Invergo, Brandon M, Daniele Dell'Orco, Ludovica Montanucci, Karl-Wilhelm Koch, and Jaume Bertranpetit (2014). "A comprehensive model of the phototransduction cascade in mouse rod cells". *Molecular bioSystems* 10.6, pp. 1481–1489.

James, Ben, Léa Darnet, José Moya-Díaz, Sofie-Helene Seibel, and Leon Lagnado (2019). "An amplitude code transmits information at a visual synapse". *Nature neuroscience* 22.7, pp. 1140–1147.

Jarsky, Tim, Mark Cembrowski, Stephen M Logan, William L Kath, Hermann Riecke, Jonathan B Demb, and Joshua H Singer (2011). "A synaptic mechanism for retinal adaptation to luminance and contrast". *Journal of Neuroscience* 31.30, pp. 11003–11015.

Järvenpää, Marko, Michael U Gutmann, Arijus Pleska, Aki Vehtari, Pekka Marttinen, et al. (2019). "Efficient acquisition rules for model-based approximate Bayesian computation". *Bayesian Analysis* 14.2, pp. 595–622.

Jiang, Bai, Tung-yu Wu, Charles Zheng, and Wing H Wong (2017). "Learning summary statistic for approximate Bayesian computation via deep neural network". *Statistica Sinica*, pp. 1595–1618.

Kastner, David B, Yusuf Ozuysal, Georgia Panagiotakos, and Stephen A Baccus (2019). "Adaptation of inhibition mediates retinal sensitization". *Current Biology* 29.16, pp. 2640–2651.

Klindt, David, Alexander S Ecker, Thomas Euler, and Matthias Bethge (2017). "Neural system identification for large populations separating "what" and "where"". *Advances in Neural Information Processing Systems*, pp. 3506–3516.

Klindt, David, Cornelius Schröder, Anna Vlasits, Katrin Franke, Philipp Berens, and Thomas Euler (2021). "Modelling functional wiring and processing from retinal bipolar to ganglion cells". *Cosyne Abstract*.

Klinger, Emmanuel, Dennis Rickert, and Jan Hasenauer (2018). "pyABC: distributed, likelihood-free inference". *Bioinformatics* 34.20, pp. 3591–3593.

Koch, Christof (2004). *Biophysics of computation: information processing in single neurons*. Oxford university press.

Kriegeskorte, Nikolaus (2015). "Deep neural networks: a new framework for modeling biological vision and brain information processing". *Annual review of vision science* 1, pp. 417–446.

Kriegeskorte, Nikolaus, Marieke Mur, and Peter A Bandettini (2008). "Representational similarity analysis-connecting the branches of systems neuroscience". *Frontiers in systems neuroscience* 2, p. 4.

Lagnado, Leon and Frank Schmitz (2015). "Ribbon synapses and visual processing in the retina". *Annual review of vision science* 1, pp. 235–262.

Lee, Meng-Jung and Günther Zeck (2020). "Electrical imaging of light-induced signals across and within retinal layers". *Frontiers in neuroscience* 14.

Lindsey, Jack, Samuel A Ocko, Surya Ganguli, and Stephane Deny (2019). "A unified theory of early visual representations from retina to cortex through anatomically constrained deep CNNs". *arXiv preprint arXiv:1901.00945*.

LoGiudice, Lisamarie and Gary Matthews (2009). "The role of ribbons at sensory synapses". *The Neuroscientist* 15.4, pp. 380–391.

Lueckmann, Jan-Matthis, Giacomo Bassetto, Theofanis Karaletsos, and Jakob H Macke (2019). "Likelihood-free inference with emulator networks". *Symposium on Advances in Approximate Bayesian Inference*. PMLR, pp. 32–53.

Lueckmann, Jan-Matthis, Jan Boelts, David S Greenberg, Pedro J Gonçalves, and Jakob H Macke (2021). "Benchmarking Simulation-Based Inference". *arXiv preprint arXiv: 2101.04653*.

Lueckmann, Jan-Matthis, Pedro J Goncalves, Giacomo Bassetto, Kaan Öcal, Marcel Nonnenmacher, and Jakob H Macke (2017). "Flexible statistical inference for mechanistic models of neural dynamics". *Advances in Neural Information Processing Systems*. Vol. 30.

Maass, Wolfgang and Anthony M Zador (1999). "Dynamic stochastic synapses as computational units". *Neural computation* 11.4, pp. 903–917.

Maheswaranathan, Niru, David B Kastner, Stephen A Baccus, and Surya Ganguli (2018). "Inferring hidden structure in multilayered neural circuits". *PLoS computational biology* 14.8, e1006291.

Marder, Eve and Adam L Taylor (2011). "Multiple models to capture the variability in biological neurons and networks". *Nature neuroscience* 14.2, pp. 133–138.

Marin, Jean-Michel, Pierre Pudlo, Arnaud Estoup, and Christian Robert (2018). "Likelihood-free model choice". *Handbook of Approximate Bayesian Computation*, p. 153.

Marr, David (1982). "Vision: A computational investigation into the human representation and processing of visual information".

Marvin, Jonathan S, Bart G Borghuis, Lin Tian, Joseph Cichon, Mark T Harnett, Jasper Akerboom, Andrew Gordus, Sabine L Renninger, Tsai-Wen Chen, Cornelia I Bargmann, et al. (2013). "An optimized fluorescent probe for visualizing glutamate neurotransmission". *Nature methods* 10.2, pp. 162–170.

Masland, Richard H (2001). "The fundamental plan of the retina". *Nature neuroscience* 4.9, pp. 877–886.

Masland, Richard H (2012). "The neuronal organization of the retina". *Neuron* 76.2, pp. 266–280.

Mauss, Alex S, Anna Vlasits, Alexander Borst, and Marla Feller (2017). "Visual circuits for direction selectivity". *Annual review of neuroscience* 40, pp. 211–230.

McIntosh, Lane, Niru Maheswaranathan, Aran Nayebi, Surya Ganguli, and Stephen Baccus (2016). "Deep learning models of the retinal response to natural scenes". *Advances in neural information processing systems*, pp. 1369–1377.

Meier, April, Ralph Nelson, and Victoria P Connaughton (2018). "Color processing in zebrafish retina". *Frontiers in cellular neuroscience* 12, p. 327.

Moser, Tobias, Chad P Grabner, and Frank Schmitz (2020). "Sensory processing at ribbon synapses in the retina and the cochlea". *Physiological reviews* 100.1, pp. 103–144.

Narayanan, Sathish (2018). "Engineering a Multi-Electrode Patch Clamp System: A novel tool to quantify retinal circuits". *Master Thesis*. `https://aaltodoc.aalto.fi/bitstream/handle/123456789/30115/master_Narayanan_Sathish_2018.pdf?sequence=2`. Accessed 24.3.2021.

Neher, Erwin and Bert Sakmann (1976). "Single-channel currents recorded from membrane of denervated frog muscle fibres". *Nature* 260.5554, pp. 799–802.

Nevala, NE and T Baden (2019). "A low-cost hyperspectral scanner for natural imaging and the study of animal colour vision above and under water". *Scientific reports* 9.1, pp. 1–14.

Obien, Marie Engelene J, Kosmas Deligkaris, Torsten Bullmann, Douglas J Bakkum, and Urs Frey (2015). "Revealing neuronal function through microelectrode array recordings". *Frontiers in neuroscience* 8, p. 423.

Ocko, Samuel A, Jack Lindsey, Surya Ganguli, and Stephane Deny (2018). "The emergence of multiple retinal cell types through efficient coding of natural movies". *bioRxiv*, p. 458737.

Oesterle, Jonathan, Christian Behrens, Cornelius Schröder, Thoralf Herrmann, Thomas Euler, Katrin Franke, Robert G Smith, Guenther Zeck, and Philipp Berens (2020). "Bayesian inference for biophysical neuron models enables stimulus optimization for retinal neuroprosthetics". *eLife*.

Ölveczky, Bence P, Stephen A Baccus, and Markus Meister (2007). "Retinal adaptation to object motion". *Neuron* 56.4, pp. 689–700.

Özçete, Özge D and Tobias Moser (2020). "A sensory cell diversifies its output by varying Ca2+ influx-release coupling among active zones". *The EMBO Journal*, e106010.

Ozuysal, Yusuf and Stephen A Baccus (2012). "Linking the computational structure of variance adaptation to biophysical mechanisms". *Neuron* 73.5, pp. 1002–1015.

Paninski, Liam, Eero P Simoncelli, and Jonathan W Pillow (2004). "Maximum likelihood estimation of a stochastic integrate-and-fire neural model". *Advances in Neural Information Processing Systems*, pp. 1311–1318.

Papamakarios, George and Iain Murray (2016). "Fast ϵ-free inference of simulation models with bayesian conditional density estimation". *Advances in Neural Information Processing Systems*, pp. 1028–1036.

Papamakarios, George, Eric Nalisnick, Danilo Jimenez Rezende, Shakir Mohamed, and Balaji Lakshminarayanan (2019a). "Normalizing flows for probabilistic modeling and inference". *arXiv preprint arXiv: 1912.02762*.

Papamakarios, George, Theo Pavlakou, and Iain Murray (2017). "Masked autoregressive flow for density estimation". *arXiv preprint arXiv: 1705.07057*.

Papamakarios, George, David Sterratt, and Iain Murray (2019b). "Sequential neural likelihood: Fast likelihood-free inference with autoregressive flows". *The 22nd International Conference on Artificial Intelligence and Statistics*. PMLR, pp. 837–848.

Peng, Yangfan, Franz Xaver Mittermaier, Henrike Planert, Ulf Christoph Schneider, Henrik Alle, and Jörg Rolf Paul Geiger (2019). "High-throughput microcircuit analysis of individual human brains through next-generation multineuron patch-clamp". *Elife* 8, e48178.

Pillow, Jonathan W, Jonathon Shlens, Liam Paninski, Alexander Sher, Alan M Litke, EJ Chichilnisky, and Eero P Simoncelli (2008). "Spatio-temporal correlations and visual signalling in a complete neuronal population". *Nature* 454.7207, pp. 995–999.

Pitkow, Xaq and Markus Meister (2012). “Decorrelation and efficient coding by retinal ganglion cells”. *Nature neuroscience* 15.4, pp. 628–635.

Prinz, Astrid A, Dirk Bucher, and Eve Marder (2004). “Similar network activity from disparate circuit parameters”. *Nature neuroscience* 7.12, pp. 1345–1352.

Pudlo, Pierre, Jean-Michel Marin, Arnaud Estoup, Jean-Marie Cornuet, Mathieu Gautier, and Christian P Robert (2016). “Reliable ABC model choice via random forests”. *Bioinformatics* 32.6, pp. 859–866.

Qiu, Yongrong, Zhijian Zhao, David Klindt, Magdalena Kautzky, Klaudia P Szatko, Frank Schaeffel, Katharina Rifai, Katrin Franke, Laura Busse, and Thomas Euler (2020). “Mouse retinal specializations reflect knowledge of natural environment statistics”. *bioRxiv*.

Real, Esteban, Hiroki Asari, Tim Gollisch, and Markus Meister (2017). “Neural circuit inference from function to structure”. *Current Biology* 27.2, pp. 189–198.

Rey, Hernan Gonzalo, Carlos Pedreira, and Rodrigo Quian Quiroga (2015). “Past, present and future of spike sorting techniques”. *Brain research bulletin* 119, pp. 106–117.

Rieke, Fred (1999). *Spikes: exploring the neural code*. MIT press.

Robert, Christian and George Casella (2013). *Monte Carlo statistical methods*. Springer Science & Business Media.

Robert, Christian P, Jean-Marie Cornuet, Jean-Michel Marin, and Natesh S Pillai (2011). “Lack of confidence in approximate Bayesian computation model choice”. *Proceedings of the National Academy of Sciences* 108.37, pp. 15112–15117.

Roorda, Austin and David R Williams (1999). “The arrangement of the three cone classes in the living human eye”. *Nature* 397.6719, pp. 520–522.

Saltelli, Andrea, Marco Ratto, Terry Andres, Francesca Campolongo, Jessica Cariboni, Debora Gatelli, Michaela Saisana, and Stefano Tarantola (2008). *Global sensitivity analysis: the primer*. John Wiley & Sons.

Scala, Federico, Dmitry Kobak, Matteo Bernabucci, Yves Bernaerts, Cathryn René Cadwell, Jesus Ramon Castro, Leonard Hartmanis, Xiaolong Jiang, Sophie Laturnus, Elanine Miranda, et al. (2020). “Phenotypic variation of transcriptomic cell types in mouse motor cortex”. *Nature*, pp. 1–7.

Schnapf, JL, BJ Nunn, M Meister, and DA Baylor (1990). “Visual transduction in cones of the monkey Macaca fascicularis.” *The Journal of physiology* 427.1, pp. 681–713.

Schreyer, Helene Marianne and Tim Gollisch (2020). “Nonlinearities in retinal bipolar cells shape the encoding of artificial and natural stimuli”. *BioRxiv*.

Shah, Nishal P, Nora Brackbill, Colleen E Rhoades, Alexandra Kling, Georges Goetz, Alan Litke, Alexander Sher, Eero P Simoncelli, and EJ Chichilnisky (2019). “Inference of nonlinear spatial subunits by spike-triggered clustering in primate retina”. *bioRxiv*, p. 496422.

Shi, Qing, Pranjal Gupta, Alexandra K Boukhvalova, Joshua H Singer, and Daniel A Butts (2019). "Functional characterization of retinal ganglion cells using tailored nonlinear modeling". *Scientific reports* 9.1, pp. 1–12.

Simoncelli, Eero P and Bruno A Olshausen (2001). "Natural image statistics and neural representation". *Annual review of neuroscience* 24.1, pp. 1193–1216.

Sinha, Raunak, Mrinalini Hoon, Jacob Baudin, Haruhisa Okawa, Rachel OL Wong, and Fred Rieke (2017). "Cellular and circuit mechanisms shaping the perceptual properties of the primate fovea". *Cell* 168.3, pp. 413–426.

Sisson, Scott A, Yanan Fan, and Mark Beaumont (2018). *Handbook of approximate Bayesian computation*. CRC Press.

Sokoloski, Sacha, Amir Aschner, and Ruben Coen-Cagli (2020). "Modelling the neural code in large populations of correlated neurons". *bioRxiv*.

Specht, Elizabeth A, Esther Braselmann, and Amy E Palmer (2017). "A critical and comparative review of fluorescent tools for live-cell imaging". *Annual review of physiology* 79, pp. 93–117.

Spira, Micha E and Aviad Hai (2013). "Multi-electrode array technologies for neuroscience and cardiology". *Nature nanotechnology* 8.2, p. 83.

Sterling, Peter and Gary Matthews (2005). "Structure and function of ribbon synapses". *Trends in neurosciences* 28.1, pp. 20–29.

Szatko, Klaudia P, Maria M Korympidou, Yanli Ran, Philipp Berens, Deniz Dalkara, Timm Schubert, Thomas Euler, and Katrin Franke (2020). "Neural circuits in the mouse retina support color vision in the upper visual field". *Nature communications* 11.1, pp. 1–14.

Szel, A, P Röhlich, AR Gaffé, B Juliusson, G v Aguirre, and T Van Veen (1992). "Unique topographic separation of two spectral classes of cones in the mouse retina". *Journal of Comparative Neurology* 325.3, pp. 327–342.

Tanaka, Hidenori, Aran Nayebi, Niru Maheswaranathan, Lane McIntosh, Stephen A Baccus, and Surya Ganguli (2019). "From deep learning to mechanistic understanding in neuroscience: the structure of retinal prediction". *arXiv preprint arXiv:1912.06207*.

Tejero-Cantero, Alvaro, Jan Boelts, Michael Deistler, Jan-Matthis Lueckmann, Conor Durkan, Pedro J Gonçalves, David S Greenberg, and Jakob H Macke (2020). "Sbi: a toolkit for simulation-based inference". *Journal of Open Source Software* 5.52, p. 2505.

Tennøe, Simen, Geir Halnes, and Gaute T Einevoll (2018). "Uncertainpy: a python toolbox for uncertainty quantification and sensitivity analysis in computational neuroscience". *Frontiers in neuroinformatics* 12, p. 49.

Toni, Tina and Michael PH Stumpf (2010). "Simulation-based model selection for dynamical systems in systems and population biology". *Bioinformatics* 26.1, pp. 104–110.

Vaz, A Ismael F and Luís N Vicente (2007). "A particle swarm pattern search method for bound constrained global optimization". *Journal of Global Optimization* 39.2, pp. 197–219.

Virtanen, Pauli, Ralf Gommers, Travis E Oliphant, Matt Haberland, Tyler Reddy, David Cournapeau, Evgeni Burovski, Pearu Peterson, Warren Weckesser, Jonathan Bright, et al. (2020). "SciPy 1.0: fundamental algorithms for scientific computing in Python". *Nature methods* 17.3, pp. 261–272.

Wang, Guangfu, Daniel R Wyskiel, Weiguo Yang, Yiqing Wang, Lana C Milbern, Txomin Lalanne, Xiaolong Jiang, Ying Shen, Qian-Quan Sun, and J Julius Zhu (2015). "An optogenetics-and imaging-assisted simultaneous multiple patch-clamp recording system for decoding complex neural circuits". *Nature protocols* 10.3, pp. 397–412.

Wang, Kun, Burkhard Arrenberg, Julian Hinz, and Aristides B Arrenberg (2021). "Reduction of visual stimulus artifacts using a spherical tank for small, aquatic animals". *Scientific reports* 11.1, pp. 1–14.

Westö, Johan and Petri Ala-Laurila (2020). "Seeing Beyond Violet: UV Cones Guide High-Resolution Prey-Capture Behavior in Fish". *Neuron* 107.2, pp. 207–209.

Wood, Simon N (2010). "Statistical inference for noisy nonlinear ecological dynamic systems". *Nature* 466.7310, pp. 1102–1104.

Wu, Michael C-K, Stephen V David, and Jack L Gallant (2006). "Complete functional characterization of sensory neurons by system identification". *Annu. Rev. Neurosci.* 29, pp. 477–505.

Yamins, Daniel LK, Ha Hong, Charles F Cadieu, Ethan A Solomon, Darren Seibert, and James J DiCarlo (2014). "Performance-optimized hierarchical models predict neural responses in higher visual cortex". *Proceedings of the national academy of sciences* 111.23, pp. 8619–8624.

Zeck, Günther, Florian Jetter, Lakshmi Channappa, Gabriel Bertotti, and Roland Thewes (2017). "Electrical imaging: investigating cellular function at high resolution". *Advanced Biosystems* 1.11, p. 1700107.

Zhao, Zhijian, David A Klindt, André Maia Chagas, Klaudia P Szatko, Luke Rogerson, Dario A Protti, Christian Behrens, Deniz Dalkara, Timm Schubert, Matthias Bethge, et al. (2020). "The temporal structure of the inner retina at a single glance". *Scientific reports* 10.1, pp. 1–17.

Zhou, Mingyi, John Bear, Paul A Roberts, Filip K Janiak, Julie Semmelhack, Takeshi Yoshimatsu, and Tom Baden (2020). "Zebrafish retinal ganglion cells asymmetrically encode spectral and temporal information across visual space". *Current Biology* 30.15, pp. 2927–2942.

Zimmermann, Maxime JY, Noora E Nevala, Takeshi Yoshimatsu, Daniel Osorio, Dan-Eric Nilsson, Philipp Berens, and Tom Baden (2018). "Zebrafish differentially process color across visual space to match natural scenes". *Current Biology* 28.13.

Zimmermann, M.J.Y., A. Maia Chagas, P. Bartel, S. Pop, L.L. Prieto-Godino, and T. Baden (2020). “LED Zappelin’: An open source LED controller for arbitrary spectrum visual stimulation and optogenetics during 2-photon imaging”. *HardwareX* 8, e00127.

Statement of Contributions

Study I: Approximate Bayesian Inference for a Mechanistic Model of Vesicle Release at a Ribbon Synapse

Journal/Conference: Advances in Neural Information Processing Systems (2019)
Authors: **Cornelius Schröder***, Ben James*, Leon Lagnado, and Philipp Berens (*equal contribution)

Contributions of the authors:
The manuscript was conceptualised and developed by **C.S.**, B.J. and P.B.; **C.S.** and B.J. developed the model and the algorithms with input from P.B.; B.J. ran 2p-experiments with input from L.L.; **C.S.** performed the final analysis and prepared the figures with input from B.J. and P.B.; **C.S.**, B.J. and P.B. wrote the manuscript.

Study II: System Identification with Biophysical Constraints: A Circuit Model of the Inner Retina

Journal/Conference: Advances in Neural Information Processing Systems (2020)
Authors: **Cornelius Schröder***, David Klindt*, Sarah Strauss, Katrin Franke, Matthias Bethge, Thomas Euler, and Philipp Berens (*equal contribution)

Contributions of the authors:
C.S. and D.K. designed the study, with input from K.F., T.E. and P.B.; **C.S.** and D.K. implemented and trained the model; D.K. generated the predictions and performed the generalization tests; **C.S.** performed the anatomical comparisons with input from S.S.; K.F. performed the in vitro experiments, **C.S.** performed in silico experiments with input from K.F.; **C.S.**, D.K., and P.B. wrote the manuscript with input from T.E., K.F., S.S. and M.B.

Study III: Fovea-like Photoreceptor Specializations Underlie Single UV Cone Driven Prey-Capture Behavior in Zebrafish

Journal/Conference: Neuron (2020)
Authors: Takeshi Yoshimatsu, **Cornelius Schröder**, Noora E Nevala, Philipp Berens, and Tom Baden

Contributions of the authors:
T.Y. and T.B. designed the study, with input from **C.S.** and P.B.; T.Y. generated novel lines and performed all data collection and pre-processing except for behavioral experiments, with input from T.B.; N.E.N. performed and analyzed behavioral experiments; T.Y. and **C.S.** analyzed transcriptomic data; **C.S.** computed information rates and deconvolutions; T.Y. and P.B. performed statistical analysis; and T.Y. and T.B. wrote the manuscript, with input from all authors.

Study IV: Distinct Synaptic Transfer Functions in Same-Type Photoreceptors

Journal/Conference: Elife (2021)
Authors: **Cornelius Schröder**, Takeshi Yoshimatsu, Jonathan Oesterle, Philipp Berens, and Tom Baden

Contributions of the authors:
The manuscript was conceptualised and developed by **C.S.**, T.Y., T.B. and P.B.; **C.S.** established the models and together with J.O. adapted the inference method; T.Y. performed electron microscopy and two-photon imaging, pre-processing of the data and generated transgenic lines, with support from TB.; **C.S.** performed additional analyses and statistical testing, with help from P.B.; T.B..and P.B. supervised the project; The manuscript was written by **C.S.** and T.B. with input from T.Y. and P.B.; Funding was acquired by T.B., P.B. and T.Y..

Study V: Ancestral Circuits for Vertebrate Color Vision Emerge at the First Retinal Synapse

Journal/Conference: Science Advances (2021)
Authors: Takeshi, Yoshimatsu, Philipp Bartel, **Cornelius Schröder**, Filip K Janiak, Francois St-Pierre, Philipp Berens, and Tom Baden

Contributions of the authors:
T.Y., P.Ba. and T.B. designed the study, with input from **C.S.**, F.K.J. and P.Be. T.Y. generated novel lines and performed 2-photon data collection and pre-processing. T.Y. also performed anatomical imaging and EM-tracing. T.Y. and **C.S.** analysed anatomical data. P.Ba. built the light-stimulator with input from F.K.J. P.Ba. also performed natural imaging data analysis, with input from T.B. and P.Be. **C.S.** performed computational modelling of the HC-cone circuit with input from P.Be. **C.S.** analysed voltage recordings with input from P.Be. **C.S.**, T.Y., P.Ba. and T.B. performed general statistical analyses, with help from P.Be. F.S.P. provided early access to ASAP plasmids. T.B. wrote the manuscript with inputs from all authors.

Acknowledgments

I thank Philipp Berens for his great supervision, all his critical feedback and his outstanding support. I thank Thomas Euler for his insightful discussions and support. I thank Julijana Gjorgjieva for her critical feedback especially in the early phase of my PhD. I thank Tom Baden and Takeshi Yoshimatsu for such productive collaborations and the long and intense discussions from different view points. I thank Ben James for his collaboration on my very first scientific paper and the great time we spent together. I thank David Klindt for being a friend, the great discussions and time we had, including working on papers, and for all projects that might come. I thank Sophie Laturnus for sharing an office space, time, joy and hassles during the long journeys to our PhDs. I thank Jan Lause and Jonathan Oesterle for their critical and fruitful discussions at all stages of my PhD. I thank Valeska Botzenhardt for her administrative support. I thank the whole Berenslab and Eulerlab for the interesting talks, discussions and shared time. I thank all members of the sustainAbility initiative, who shared their ideas, broadened my horizon and gave me so much motivation. I thank my flatmates for the intense time and their respect during home office and lockdown. I thank all my friends for being there, sharing time, joy and sorrow. I thank my parents and family for being there when I most need them, giving me the freedom and opportunity to develop into who I am now and supporting me on my life's journey. And finally, I thank Helena Tilmann for her support, her patience and for reminding me of the fundamental aspects of life.

Appendix

A Study I: Approximate Bayesian Inference for a Mechanistic Model of Vesicle Release at a Ribbon Synapse

Published as: Schröder*, James* et al. (2019) In: *Advances in Neural Information Processing Systems*. Vol. 32. pp. 7070–7080

Link

`https://proceedings.neurips.cc/paper/2019/file/0e57098d0318a954d1443e2974a38fac-Paper.pdf`

*equal contribution

B Study II: System Identification with Biophysical Constraints: A Circuit Model of the Inner Retina

Published as: Schröder*, Klindt* et al. (2020) In: *Advances in Neural Information Processing Systems*. Vol. 33. pp. 15439–15450

Link

`https://proceedings.neurips.cc/paper/2020/file/b139e104214a08ae3f2ebcce149cdf6e-Paper.pdf`

*equal contribution

C Study III: Fovea-like Photoreceptor Specializations Underlie Single UV Cone Driven Prey-Capture Behavior in Zebrafish

Published as: Yoshimatsu et al. (2020) In: *Neuron*.

Link

https://www.sciencedirect.com/science/article/pii/S0896627320303135

D Study IV: Distinct Synaptic Transfer Functions in Same-Type Photoreceptors

Published as: Schröder et al. (2021) In: *Elife*.

Link

`https://elifesciences.org/articles/67851`

E Study V: Ancestral Circuits for Vertebrate Color Vision Emerge at the First Retinal Synapse

Published as: Yoshimatsu et al. (2021) In: *Science Advances*.

Links

https://www.science.org/doi/10.1126/sciadv.abj6815

Including supplementary material.