Rapid dynamics in the retina

Baptiste Lorenzi

CentraleSupélec, Unversité Paris Saclay, Institut de la Vision

Abstract

We trained a convolutional neural network (CNN) model on large-scale functional recordings of RGC responses to natural mouse movies, and then used this model to investigate the role of past images in the activity of RGC.

Our work showcases how a combination of experiments with natural stimuli and computational modelling allows discovering ...

1 Introduction

During my internship in Olivier Marre's team at l'Institut de la Vision, I am focusing on computational modeling of the retina. Olivier Marre's team is an interdisciplinary laboratory, hosting four professors and a dozen of interns, Ph.D. students and post-docs, working hand in hand to advance research on the retina. They all have various backgrounds mainly from biology, theoretical physics and engineering. In the context of this project, I've been working closely with Samuele Virgili, a third-year Ph.D. student, whose previous and current projects all focus on the modeling of retinal ganglion cells.

The ability of the visual system to process complex stimuli on different temporal and spatial scales is remarkable. Natural environments are such complex stimuli, and extracting the relevant features at all times is crucial for many species.

Both the accessibility and apparent complexity of the retina make it a perfect candidate for the study of the front-end of visual processing [Gollisch and Meister, 2010]. In

the mouse, the retina is composed of more than 30 parallel feature channels, embodied by ganglion cell types. Through their axons, the optic nerve, they provide information to numerous visual areas in the brain. A few channels are active in the encoding of basic features including luminance changes and motion, that are only combined in more downstream areas. Other channels however are known to play a role in the extraction of specific features of natural scenes.

An important feature of natural scenes is the diversity of contrast levels in one scene. This diversity can be both spatial (plain and detailed object side to side) and temporal (sudden apparition of an object). It is known that the visual system adapts to the diversity of fluctuations in the scene. This adaptation begins in the retina. By probing the retina with flickers of different intensities, Baccus and colleagues revealed two distinct phases of sensitivity change in the retina: one fast (<0.1s) and one slow (over 10s) [Baccus and Meister, 2002]. In another study, Garvert et al. revealed that contrast adaptation also happens at different scales, either at the whole scene scale (global contrast adaptation) or within one ganglion cell receptive field, the part of the visual field that the cell receives inputs from (local contrast adaptation) [Garvert and Gollisch, 2013].

Still, we currently lack an explanation of the features extracted by many channels and how they adapt to diverse scenes. One of the historical reasons for this is that synthetic stimuli used to study retinal responses are not complex enough to activate these channels. Hence, they cannot uncover critical response properties encountered in natural environments.

In practice, Karamanlis and colleagues [Kim et al., 2020] have probed a larger complexity in retinal spatial non-linearities thanks to stimuli capturing the statistics of natural environments. As those non-linearities cannot be captured by Linear-Nonlinear (LN) models, convolutional neural networks (CNNs) have become the state-of-the-art approach

for predictive modeling of visual processing, not only in the retina but also in higher visual areas [McIntosh et al., 2017].

Insight on methods Here, we combined the power of CNN-based modeling with large-scale mutli-electrode array (MEA) recordings from RGCs to investigate the mechanisms of fast adaptation in the retina under natural stimulus conditions. To this end, we recorded RGC responses to flashed images paired together. Each pair is composed of a synthetic adaptation image followed by a natural image. We were able to identify different trends in the responses of RGCs to natural images, depending on the adaptation image.

To investigate the diversity of this adaptation process and its implementation, we paired deep convolutional models with more traditional modeling. We trained a CNN model on RGC responses to a movie of flashed images. After training, we study how this model generalized to images after being adapted with patterns it wasn't trained to. By tweaking part of the model at the inference level, We hope to show that temporal mechanisms such as gain-control play a major role in the fast adaptation of RGCs in a natural context.

2 Background

The retina. In vertebrates, the retina is part of the central nervous system. It consists of just a few layers of neurons, each with a distinct role in processing visual information **??**. ADD FIGURE ON THE STRUCTURE OF THE RETINA

At its forefront are photosensitive neurons known as photoreceptors, which serve as the initial light sensors within this neural network. ADD ABOUT CONES AND RODS

These photoreceptors stimulate bipolar cells, a diverse group comprising 15-20 anatomical distinct types in the mouse. They all exhibit unique responses to visual stimuli, with

an even larger functional complexity than anatomical diveristy.

The bipolar cells, in turn, excite retinal ganglion cells (RGC), the final relay in the chain, which then transmit the pre-processed visual data to the rest of the brain via the optic nerve. RGC of the same type are described as sharing the same physiology morphology, intra-retinal connectivity, retinal mosaic and genetic markers. It is not yet known if such biological markers are enough to define the variety of functional output channels of the retina. According to Baden and co-worker, there should be at least 32 different RGC functional types [**?**]. An example of functional diversity in the RGC groups is their preference for local light increase and/or decrease. They are respectively refered as ON, OFF and ON-OFF RGC.

Additionally, the retina hosts two families of inhibitory neurons: horizontal and amacrine cells. These neurons play a crucial role in modulating the activity of excitatory cells, adding another layer of complexity to the visual processing within the retina.

Compared to the rest of the brain, the retina is relatively simple, making it an ideal neural tissue for in-depth study using computational models. Its accessibility for experimental research further enhances its appeal as a valuable subject for investigating neural code and neural processes.

Standard model of the retina.

Adaptation in the retina To operate optimally in a wide range of stimulation conditions, the retina adapts its responses to the statistics of the visual scene. In particular, it was observed to adapt to the average luminance as well as the range of intensity fluctuations about the mean, referred to as the contrast of the scene.

Visual systems can function over a wide range of light intensities, from starlight to a bright sunny day – a luminance range of 10 10 The retinal adaptation to the luminance of the scene is quite simple by nature. For instance, it is known that the retina uses different

neuronal pathways at low and high luminance. Rods and their retinal neuronal channels cover the dimmest light while cones facilitate contrast, color and motion discrimination but only in brighter light.

In a high-contrast environment, RGC tends to be more much less sesnsitive than in low contrast envrionment ???. This sensivity adaptation happens on different timescales. A large change in stimulus contrast wouldn't change the response properties of cones and horizontal cells . But it would change the behaviour of bipolar cells, meaning fast adaptation to contrast begin in their sublayer. This almost immediate effect of a contrast increment changes the the property of some bipolar cells, including their temporal patterns as well as their selectivity. Their diverse response to this contarst increment is correlated to the diversity of functional and morphological subtypes among bipolar cells Baccus and Meister [2002]. This evolution is also seen in all ganglion cells.

BEEEH It is still unclear how it affects temporal processing and the sensitivity to stimulus features[Baccus and Meister, 2002].

Furthermore, contrast adaptation can also happen at different scales, either at the whole scene scale (global contrast adaptation) or within one ganglion cell receptive field, the part of the visual field that the cell receives inputs from (local contrast adaptation) [Garvert and Gollisch, 2013]. Local contrast adaptation is especially relevant in understanding how ganglion cells respond to natural images since these stimuli are full of spatial details like edges in which two contrast levels appear simultaneously. Such images are challenging to use, as they can't be summed up to a few statistics easily.

Retinal response to natural images.

Most of the knowledge we have on the retinal response comes from experiments using syntheical stimuli that doesn't reflect the full diversity of natural scenes that the mouse retina evloved to respond to.

Convolutional Neural Networks.

Due to the large statistical complexity of natural scenes, convolutional neural networks have grown to be a new standard for modeling retinal responses to natural images. However, compared to baseline models, they tend to be harder to read from a biological perspective. Hence there is an ongoing debate in the field on the limitations of those models in the context of the study of the retina. We believe that with careful modeling decisions, it is possible to learn a lot from those models, especially regarding local and temporal dynamics.

CNNs have also been used to describe the cortex response to natural images **?**. The amount of available cortex data even led to the development of a 'foundation model' of the mouse visual cortex with a remarkable capacity to generalize to various stimulus domains **?**. TO ADD

While CNNs modeling prowess can be measured using traditional metrics such has their ability to predict the average spiking rate response of a ganglion cell to a given image, it's hard to pinpoint what is missing in their predictions.

3 Methods

This work is in some ways a continuation of Goldin et al. [2022], from which we derived most of the methods presented here. By comparison, this time we take account of temporal dynamics in the responses. The switch from 2D visual inputs to 3D spatio-temporal inputs complexifies every steps of the analysis but is ... COMPLETE

Retinal recordings. Since I don't realize any experiments myself, I will try here to give as few details as necessary for the understanding of the rest of the work. Still, experimental recording of the retina is a very interesting topic and the reader can look here for more information. The laboratory has access to three experimental rooms that

enable state-of-the-art experimentation on the retina. For this project, we record the activity of retinal ganglion cells using a multi-electrode array. The retina is placed on a ???

Stimuli design. The stimuli used in this project are composed of two images, one synthetic adaptation image followed by a natural image. Adaptation images are taken from a pull of three different patterns: a grey screen used as control, a checkerboard of X*X checks and the same checkerboard with inverted colors (Fig. TO ADD). Natural images are taken from ADD REFERENCE. XXXX images were used for training the CNN, 10 were used to test the CNN and among them, 3 were used to record an estimation of the LSTA of each cell. Adaptation and natural images are always paired together to form a single stimulus pair, also referenced as a clip. Each frame is XXXxXXX pixels wide and each clip is 2*400ms long.

The training set is composed of XXXX clips, each composed of the grey adaptation image followed by a natural image. The test set is composed of 30 clips, each repeated 30 times. The test clips are composed of 10 different natural images preceded by each adaptation (3 different clips for each natural image). The dataset used to record LSTA is composed of 9 different clips repeated 1000 times. Each clip is composed of one of the three selected natural images preceded by one of the adaptation patterns.

We first used 4 different natural images while computing the LSTA of each cell, each 12 different clips being repeated 12 times. We found that the estimation of the LSTA was too unstable with only 750 repetitions. In following experiments we excluded the image that yielded the least amount of stable estimations of LSTA (20% average success rate as compared to 42% average success rate for the other three images). We then used 3 different natural images while computing the LSTA of each cell, each 9 different clips being repeated 1000 times. We found that the estimation of the LSTA was stable with

1000 repetitions.

Data processing. Multi-electrode array experimental data takes the shape of a collection of temporal electrical signals tiling the recorded area. In most scenarios, including here, these signals are sorted into different cell signals using a semi-automatic algorithm. This algorithm is based on the shape of the electrical spikes as well as their spatial location. It is quite messy due to the low signal-to-noise ratio in the data and each experiment needs to have its sorting corrected by hand. This process can take up to an entire day for a single experiment. I used spiking-circus for semi-automatic spike sorting and the UI phy for handmade corrections. [CITE] It is important to note that even though the retina is an easier organ than most to record clean spike signals from, the data is still very noisy and the sorting process is not perfect. Hence, when validating hypotheses, cells are usually rated by their reliability.

After spike sorting, we analyze the recording from standard stimuli to characterize each ganglion cell receptive field. To this end, we display a random binary checkerboard for approximately 1 h at 30 Hz. Check size is 42. A ganglion cell receptive is computed as its spike trigger average (STA), for this checkerboard stimulus. The STA of a cell can also be described as the stimulus that triggers the most spikes from that cell. It is computed as the average of the presented checkerboard weighted by the number of spikes using a set number of samples per repetition (here 21). The spatial STA is usually shown as the 2-dimensional spatial slice at the maximum value after smoothing. Temporal STA is the one dimensional time slice at the pixel with the maximum value. For smoothing, a double Gaussian is fitted on the resulting spatial STA.

Natural images. We used a subset of the Open Access van Hateren Natural Images Dataset [ADD TO BIB]. It consists of monochromatic and calibrated (perfect mapping from pixel value to luminance) images of diverse natural environments. These images need

to be preprocessed to avoid triggering the adaptation to different ranges of light intensities in the retina, which would call unwanted dynamics. First, images with numerous saturated pixels were not included in our subset. Using a custom procedure previously developed in the laboratory, we then ensured the images were normalized in the mean luminance and the root mean square (RMS) contrast.

LSTA. To record the local specoficity of the response of a ganglion cell to a natural image, we used a method called local spike trigger average (LSTA) for its analogy with the STA. This method was previously developed in the laboratory. We first generate a set of perturbed natural images by superimposing some of the natural images (3-4 images) with various perturbation patterns in the form of random checkerboards. We once again used a checker size of 42. Following calibration guidelines measures in previous experiments, the amplitude of the perturbation was set to 12.5%, where 100% corresponds to a pixel value of 1. In the mouse retina, this amplitude was found to trigger a change in firing rate of approximately 1.5Hz in ganglion cells with high firing rates to the unperturbed images [Goldin et al., 2022].

Data visualization. Due to the diversity of the data we work with, it can be challenging to have all the relevant information on one screen. First, it's important to always have the rasterplot in sight since it informs of the quality of the cell at a glance. I u

Data selection. Not all recorded cells are suitable for all types of analysis. Overall, the main quality we look for in a cell is its stability during an entire stimulus clip. It reflects its health and likeliness to behave normally during the presentation. For our most complex experimentations, cells need to remain stable in-vitro for up to five hours, which is quite unlikely. In Fig. , we describe the different selection steps and their influence on the amount of usable data. Tp

Blablable to share my programming skills to help and improve the data pipeline of

the laboratory.

Modeling. This should be the main part of my internship and also the most challenging. We are designing a dynamical model of the retinal fast adaptation. In fact, we mostly look at the evolution of the response from an image to another, meaning that the dynamic we observe only spans two points in time. This reduction makes the model more realistic to study. Most of this job can be summarized as model design, python programming, sensitivity analysis and data fitting. By comparing how different modeling strategies reproduce the observed LSTA in the data, we can gain insight on how fast adaptation to natural scene is implemented in the retina.

Our baseline model is the LNLN model of ganglion cell widely used in the literature. Each neuron is encoded as a spatial linear filter chained with a non-linearity (usually an activation linearity in the like of ReLU). A single layer of subunit neurons, representing bipolar cells, converge into a single modeled ganglion cell. We would like to add temporal dynamics to this model, either by adding a time dimension to the spatial liner filter of the cells or by considering a gain control mechanism. This last mechanism consists in scaling up or down the present output depending on past outputs (Figure TO FIND).

We will first study our models in a data agnostic manner and study its behavior for different set of parameters. We will then fit it on our own experimental data using an efficient optimization framework in python using strategies developed in the field of machine learning.

4 Results

Some idea of speech: *** responses of exemplary RGCs

Here, we investigated fast adaptation in the mouse retina under natural stimulus conditions. To this end, we trained a CNN model on RGC responses to a movie of flashed

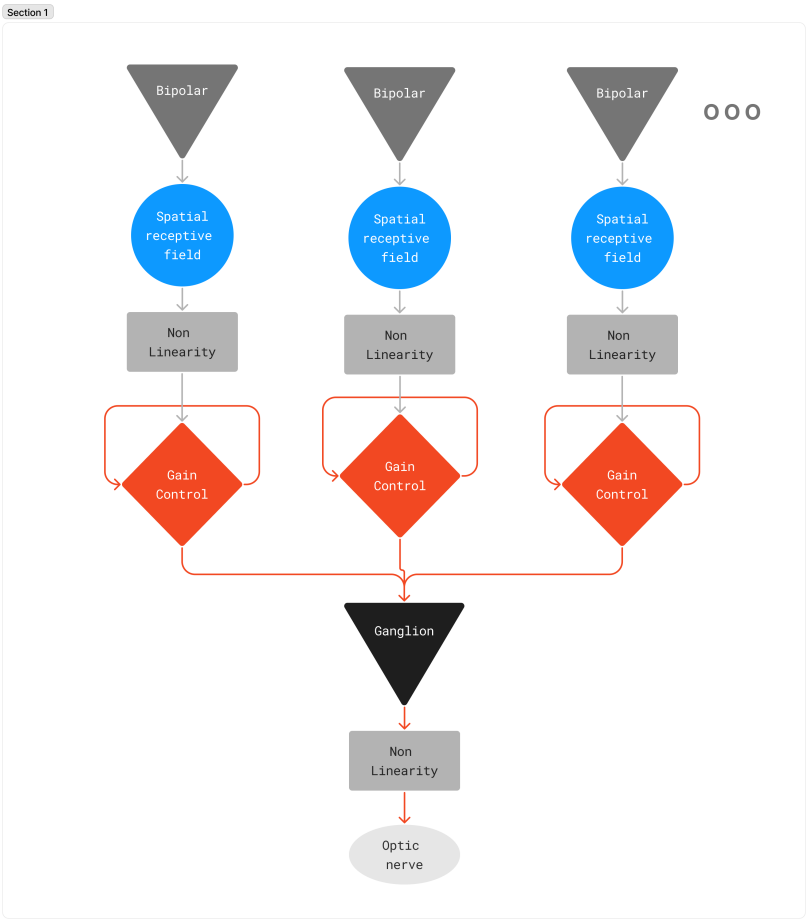

Figure 1: **Quick sketch of a gain control LNLN model.** Each bipolar cell is composed of a linear spatial filter that selectively responds to part of the scene, a non-linear activation function, and a gain control mechanism that scale its output depending on past events. They all converge into on bipolar cell (forming its receptive field) of which output is also modeled using a non-linear function.

images appearing naturally in the mouse environment,

5 Conclusion

We observed that during natural image stimulation, many ganglion cells change their selectivity for different parts of the images depending on previous light patterns.

We combined large-scale recordings of RGC responses to natural movie stimulations with CNN-based modeling to investigate such mechanisms of fast contrast adaptation in the retina.

Under realistic regularization constraints, the CNNs learned a structure similar to retinal pathways, where a ganglion cell activation is the result of a pooling of local subunits of different types in a specific area in space, the ganglion cell receptive field.

Our result supports the idea that retinal ganglion cells encode both spatial and temporal features of natural scenes on a local scale. Previous works have described those features to be encoded as features of the retinal response (latency, firing rate). We might be able to support this theory with further comparison of measured responses with predicted responses of our model.

TO DO

Maheswaranathan and colleagues [Maheswaranathan et al., 2023] have recently been able to predict different aspect of encoding in the retina using deep comvolutional network. In comparison, our experimental approach of estimating the LSTA allow a direct comparison from the model to the data. Classical estimation of performance can't describe what is missed in the prediction, while our qualitative comparison might be able to.

The modeling of retinal responses to natural stimuli has improved our understanding of complex retinal processing. In a recent review, Karamanlis and colleagues /citep,

suggested three perspectives of study on the retinal encoding of natural scenes: The circuit perspective ('How is the retinal code implemented?'), the normative perspective ('Why is it complimented this way?) and the coding perspective ('What is the code used by the retina?'). In this work, We focus on the 'what'. By exploring the response of the retina to a portion of the spatio-temporal stimuli space we can gain insight into the code used by the retina on that subspace. To explore further the 'how' perspective, one would need to study how the different known types of cells in the retina participate in that encoding. This poses the challenge of bridging the typing of cells from functional and anatomical perspectives. The normative perspective has also been explored using deep CNNs with anatomically realistic constrained. It is likely that species with simpler cortical circuitry, as mice, have a stronger need for upstream feature extraction, in the retina. In opposition, species with computationally powerful cortexes such as primates can deal with more faithful and linear representations of the visual inputs. Some studies admirably developed approaches that allow investigation of retinal processing from all three perspectives [ADD CITE].

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Supplementary materials