ON and OFF Pathways of Ganglion Cells in the Salamander Retina

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One of the main goals in neuroscience is to explain the computation and functional role of sensory neurons and its connection to the underlying biological mechanisms. In the vertebrate retina, various statistical structure of the visual scene is transformed, decomposed and encoded through the signal processing in the inner retinal circuitry to ganglion cells. A certain ganglion cell receives a combination of excitatory and inhibitory inputs from many presynaptic neurons, where the inputs can be represented as the average response from On-type and Off-type bipolar cells. To understand the biological circuit structure, a parallel two-pathway Linear-Nonlinear(LN) model is used to capture the average features represented by each pathway. Here, I applied machine learning approaches to find the two-pathway LN model that best represents the ganglion cell's circuitry.

1. Introduction

In neuroscience, a central research problem is to understand the mathematical description between the stimulus and response of sensory neurons and its relationship to the underlying biological circuit structure. One widespread approach to this problem is to use a simple quantitative model, mapping the stimulus and the neuronal response. In the early visual system, specifically in the retina, the problem is to describe the relationship between the retinal neural activity and the light intensity as a function of time, space and wavelength. One of the main interests is to have a compact description that predicts the response of ganglion cells, known as spikes. Having such description would provide a good tool in understanding what features of the visual input are encoded by the cell.
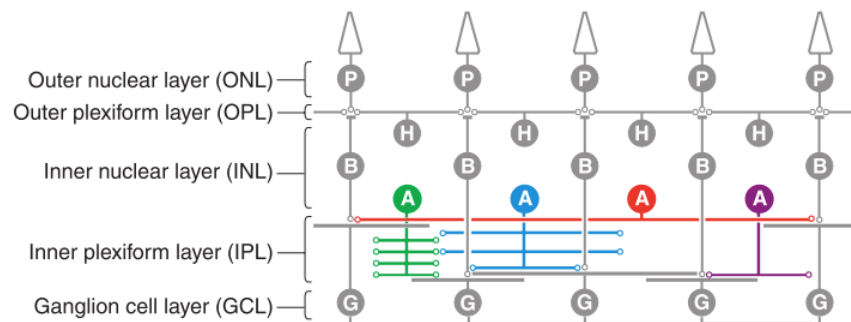

Figure 1. A schematic diagram of vertebrate retina (Baccus, 2007).
The retina encodes visual scene by transmitting light intensity into a sequence of spikes. The visual stimulus is detected in the ONL, converted into a continuous-time electrical signal. The signal is processed through the inner layers (INL and IPL) to the ganglion cell layer (GCL), and it is encoded into spikes.
P: photoreceptor, H: horizontal cell, B: bipolar cell, A: amacrine cell, G: ganglion cell.

In the vertebrate retina, the visual stimulus is converted into electrical signals by the photoreceptors, and it is processed through the inner layers to the ganglion cell layer (Figure 1). A ganglion cell receives diverse inputs from multiple interneurons, bipolar and amacrine cells, where each interneuron plays role to shape and process particular features of the visual input. The response of a ganglion cell incorporate the signal processing in the inner retinal circuitry and at the ganglion cell level, explaining selected or discarded components of the visual information (Baccus, 2007). A conventional way to understand the computation of a ganglion cell and how visual stimuli are related to the ganglion cell's response is to find a single average measure, a Linear-Nonlinear (LN) model, where a linear temporal filter is followed by a static nonlinear transformation (Figure 2e). The linear filter represents the average input stimulus feature that the cell is sensitive to, and the nonlinearity is the average instantaneous comparison between the filtered input and the cell's response (Chichilnisky, 2001). However, the underlying system is more complex that cannot be explained by a simple model.

Although the linear filter is associated with the receptive field of the ganglion cell, this single LN model explains less about the complex connectivity of inner neurons to the ganglion cell. Previous reports have shown that ganglion cells encode visual stimulation relying on parallel processing pathways, representing inputs from On-and Off-type bipolar cells (Fairhall et al. 2006; Geffen et al. 2007; Gollisch and Meister, 2008). The computation of the ganglion cell related to the visual stimulus can be modeled as having two average On- and Off-type bipolar pathways. The two pathways represent population of cells that responds to light intensity by either being activated when the lights turned on or when the lights turn off respectively. To incorporate this biological circuit structure, a parallel two-pathway LN model can be used to capture the average feature each pathway is processing (Figure 3).
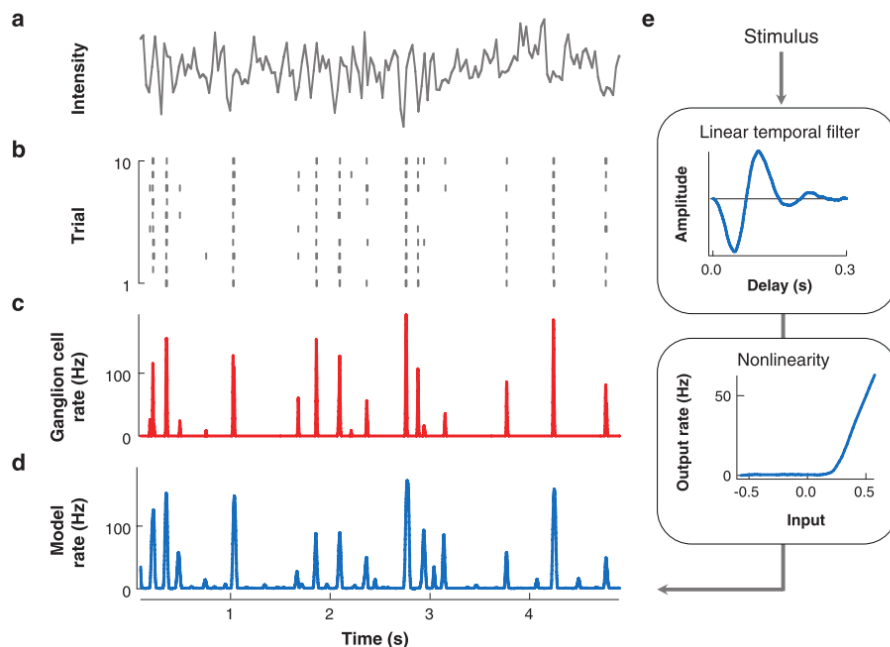

Figure 2. Modeling of Retinal Function (Baccus, 2007).
(a) Visual stimulus drawn from a White Gaussian distribution. (b) Raster plot. Spiking response of a single salamander ganglion cell to repeated stimulus sequence, recorded with a multielectrode array. Each row corresponds to a repeat, and the vertical mark represents a spike. (c) The firing rate of the cell. Peristimulus Time Histogram(PSTH). (d) The firing rate predicted by a Linear-Nonlinear(LN) model. (e) The LN model. The visual stimulus is convolved with a linear temporal filter and the output is then transformed by a static nonlinearity.
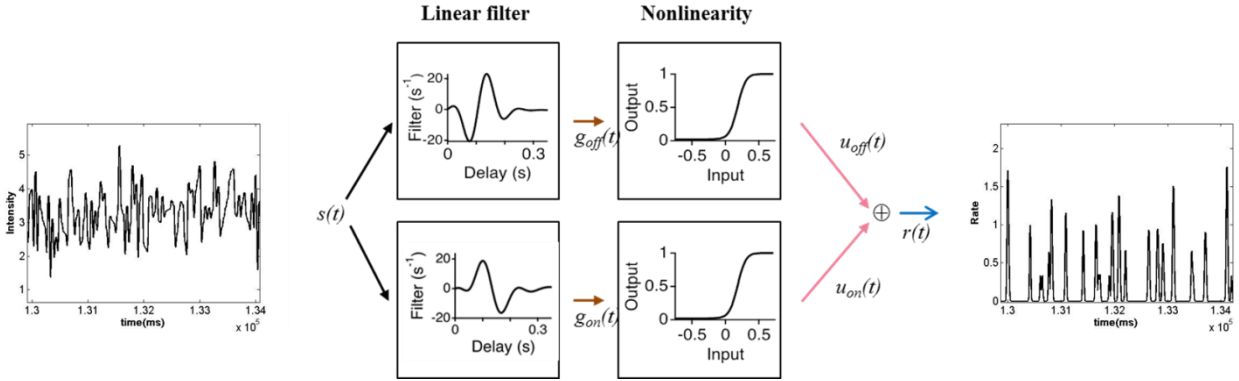
Figure 3. Parallel two-pathway Linear-Nonlinear(LN) model.
Visual light intensity denoted $s(t)$ is passed through on- and off-type biphasic filters, producing $g_{off}t)$ and $g_{on}(t)$. The filter outputs are transformed by threshold nonlinearities, and then linearly summed to produce the firing rate response. The rate is calculated by taking the average of the number of spikes in a time bin of 10ms. Top LN represents the off-pathway and the bottom is the on-type. The pathway type is defined by the filter shape. The Off-type pathway responds to the time course of light changing from negative to positive and the On-type pathway vice versa. Nonlinearity is modeled by a sigmoidal function having midpoint and slope as variable.

In this project, I generated spiking data with a two-pathway spiking model, where the linear filters of each pathway were given to match the average On- and Off-type bipolar cell pathway. My first goal was to estimate the two linear filters by correlating the spikes and the stimulus. I varied the parameters of the two-pathway spiking model to mimic the change of threshold change at the bipolar cells, and identified the different eigenvalue spectrum of the covariance matrix of the set of stimuli that elicited spikes. In addition, I performed gradient decent based optimization to fit a two-pathway LN model to the generated spike data.

2. Methods

In order to generate multiple spike trains, I used a two-pathway spiking model. The spiking model is composed of a two-pathway Linear-Nonlinear-Kinetic (LNK) model followed by a Spiking block (S) (Figure 4). The LNK model accurately captures both the membrane potential response and all adaptive properties of ganglion cells (Ozuysal and Baccus, 2012). The Spiking block consists of a decision function and a feedback loop adapted from Keat's model (Keat et al., 2001). I used a set of LNKS parameters that fit the experimental data. A set of optimal LNK parameters was used that estimated the intracellular membrane potential recording. I separately measured the Spiking block parameters that optimally captured the spikes from the intracellular membrane potential. To produce some variation in the output, the Gaussian noise was given to the spiking model to vary the timing and the number of spikes. For each trial, I generated 600s of spatially homogeneous light stimulation, $s(t)$, and passed through the LNKS model to produce multiple spike trains, $r_i(t)$. I aimed to fit the two-pathway LN model to this stimulus and spike train data sets.
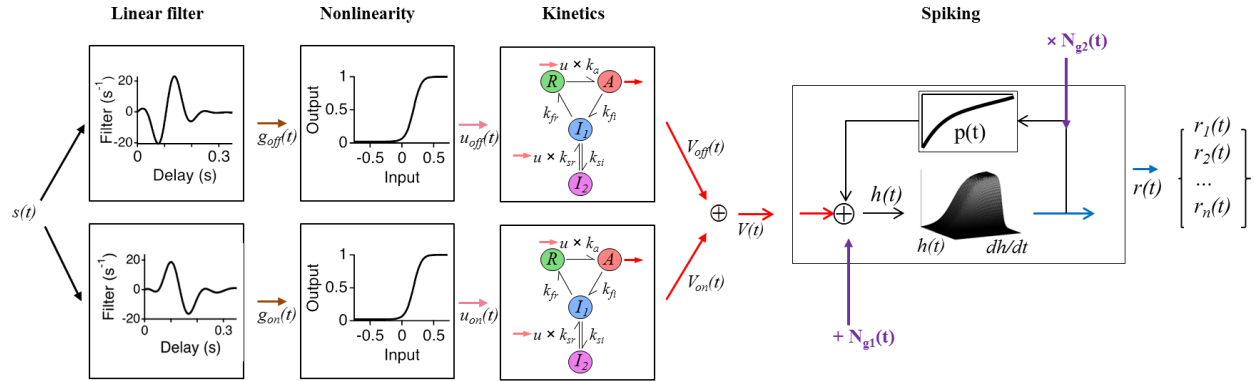
Figure 4. The two-pathway Linear-Nonlinear-Kinetic-Spiking(LNKS) model.
The input *s(t)* is passed through a linear temporal filter, a static nonlinearity and a first-order kinetic model, where the input *u(t)* scales two rate constants. The output *v(t)* is the active state A, which are passed through the decision block of the spiking block to generate spikes. For every spike, a negative exponential is fed back to v(t).

The ganglion cell response at any instant of time is determined by the stimulus sequence that the cell observed. To estimate the two On-and Off-filters of the two-pathway LN model, the spike-triggered stimulus ensemble is found (Figure 5). The ensemble consists of the set of stimulus segments that preceded the spike. The spike-triggered average (STA) stimulus is computed by taking the mean of this ensemble as shown in Figure X. To decompose the STA into two filters, I first performed spike-triggered covariance analysis to represent the ensemble in a low dimensional subspace by simply applying the principal component analysis (PCA) to the spike-triggered ensemble. The first four principal components of the ensemble generated by the LNKS model are shown in Figure 6. The input light distribution and two nonlinearities of the LNKS model shown in Figure 7a are used. Next, I applied K-means clustering algorithm to identify the means of two clusters. These two filters are compared to the filters of the LNKS model. Additionally, I changed the nonlinearity midpoint of the LNKS model to see in which situations the two pathways were possible to identify. Finally, the two-pathway LN model is found by optimizing the two pathway model to minimize the l_2-norm between the generated firing rate and the estimate using the *fmincon* function provided by MATLAB. Spikes were smoothed using a Gaussian window to get the firing rate in the optimization procedure.
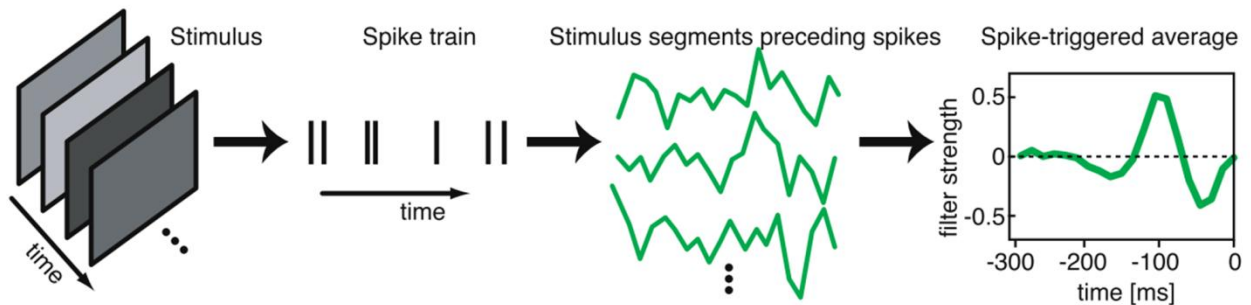

Figure 5. Light intensity and spike-triggered stimulus ensemble (Gollisch and Meister, 2008)
Spatially homogeneous light stimulus is given and it produces spikes. Spike-triggered stimulus ensemble is computed by collecting the stimulus segments preceded spikes. The average vector of this ensemble estimates the stimulus feature the cell is sensitive to (STA).

3. Results

Performing the principal component analysis to the spike-triggered ensemble (spike-triggered covariance) gives a good starting point to identify the two pathway filters. The significant principal components give the directions that the complete stimulus variance differs the most to the variance of the stimulus set that elicited spikes. Simply assigning the first two significant principal components as the filters of the two-pathway LN model, and measuring the static nonlinearities by instantaneously comparing to the firing rate may lead to a good numerical estimate of the output. However, the two filters found using PCA explains less of biophysical characterization of the inner circuitry, as expected that the nature does not choose two components to be orthogonal. The first component is a biphasic On-filter, whereas the other components seemed to be very noisy (Figure 6, Left). For comparison, the spike-triggered average (STA) and two linear filters of the LNKS model are shown (Figure 6, Right). The STA describes that the ganglion cell response is due to the light decrease followed by an increase and another decrease. It can be also thought as the inner circuitry forming off center receptive field, and having delayed effect from the surrounding receptive field. Thus, the two filters of the model should aim to capture these biological explanations of the temporal processing of the two average On- and Off-bipolar pathways.

The shapes of the two filters of LNKS model, shown in Figure 4, can be interpreted as both On- and Off-bipolar cells having biphasic processing of the spatially homogeneous visual stimulus. This is due to the fact that the stimulus excites both the receptive field center and inhibitory surround of bipolar cells. Also, the Off filters have faster kinetics, meaning that the time to the first peak is shorter than the On filters. Several studies have reported basic techniques to separate two filters that explain these On-and Off-pathway behaviors. Two clusters of the spike-triggered ensemble can be found by separating along the zero axis of the first principal component and assessed the mean of two clusters to be the filters (Fairhall et al. 2006; Gollisch and Meister 2008). In another study, K-means clustering method was used to find the center of two clusters (Geffen et al., 2007). Here, I followed the latter approach.
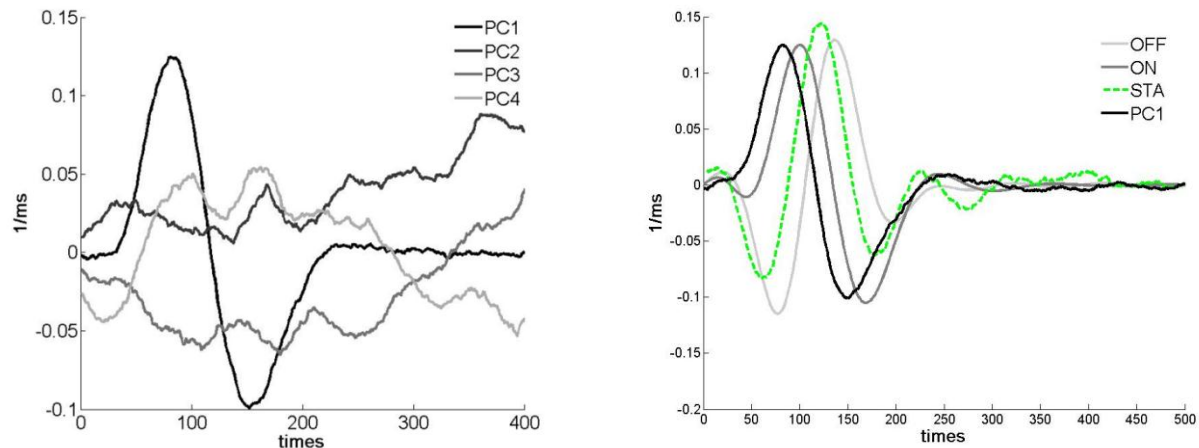

Figure 6. Principal component analysis (PCA) and the STA compared to On- and Off-filters
Left: The figure shows the first four principal components of the spike-triggered stimulus.
Right: The STA and PC1 are compared to the on and off filters of two-pathway LNKS model used to generate simulated spikes. The average response of the stimulus ensemble (STA) is indicated by the green dotted line. The black line is the first principal component. The Off- and On- filters of the LNKS model are the gray lines.
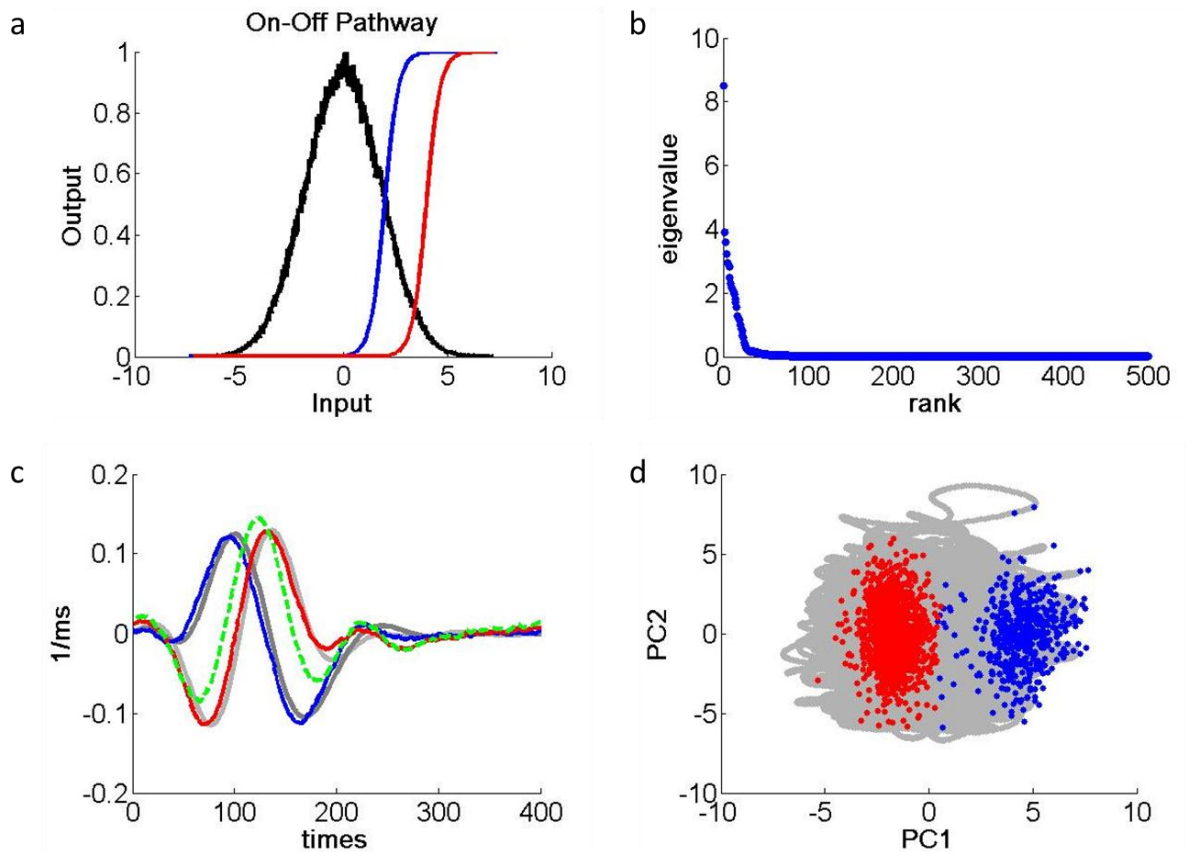
Figure 7. Identifying the two-pathway filters from spike-triggered ensemble

(a) The distribution of the input and two nonlinearities (On : red, Off: blue). Thresholds are 2 and 4.

(b) The eigenvalue spectrum of the principal component analysis. For this case, the eigenvalue of the first principal component is distinctive from other eigenvalues, where the PC1 is shown in Figure 6.

(c) On and Off linear filters. Gray filters are the ones that I used to generate the response, and blue and red filters are the recovered On and Off filters respectively. Recovered filters are the mean of each cluster shown in (d) found by K-means clustering algorithm. Dotted green is the spike-triggered average(STA).

(d) The original stimulus ensemble and the set of spike-triggered stimulus ensemble projected onto the first two principal components. Here, two clusters are distinctive; the red and blue corresponding to Off and On filters in (c). The gray dots denote the total stimulus ensemble.

Figure 7 describes the results assessed using the K-means clustering algorithm. Due to the linearity of Gaussian process, the stimulus convolved with the linear filter is also Gaussian distributed (Figure 7a). Then, the outputs of the linear filters are transformed by two different nonlinearities. The nonlinearities are sigmoidal functions having different thresholds respective to the output distribution of the filter, as shown in Figure 7a. These nonlinearities are expected to be caused by the voltage dependent calcium channels of the bipolar cells. One pathway having a higher nonlinearity threshold led to a distinctive eigenvalue compared to others, as shown in Figure 7b, and the spike-triggered ensemble clearly formed two clusters. By applying the K-means clustering algorithm to the ensemble, I was able to classify the ensemble in to two clusters. I computed the means (spike-triggered average) of two clusters, and identified two filters, as shown in Figure 7c.

Additionally, to see the effect of nonlinearity threshold playing role in recovering the two temporal filters, I have followed the same procedure to each changed nonlinearity threshold case. For simplicity, I used the same nonlinearity threshold for two pathways as shown in Figure 8. The K-means clustering algorithm failed to identify two clusters in the spike-triggered ensemble when both thresholds were low (Figure 8, first row). I increased the data size upto 1,000s, but it did not improve. Especially, by looking at the eigenvalue spectrum, as shown in the second column, K-means algorithm was not sufficient to estimate the two filters of the LNKS model, when there was no distinctive principal component. The projection of the spike-triggered stimulus ensemble onto the first two principal components also indicates that the data varies similarly to stimulus features, forming just one cluster. Thus, having both low nonlinearity threshold values explains that neither On-nor Off-pathways have strong effect on the response of the ganglion cell. In contrast, as the threshold was increased, a significant component was detected forming two distinct clusters. The third and fourth row of Figure 8 shows that the estimated two filters are very similar to that of the LNKS model.
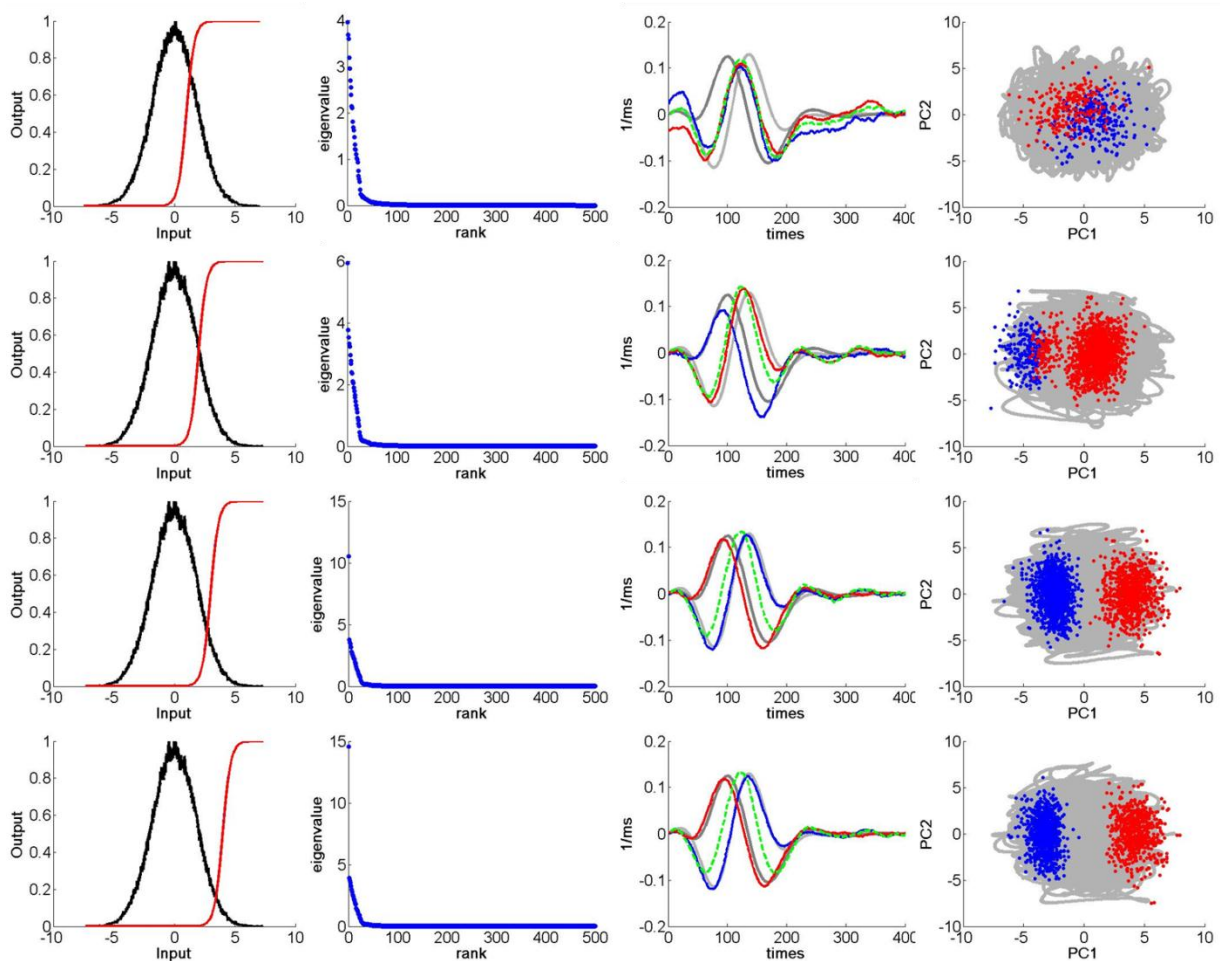

Figure 8. Identifying two-pathway filters for various nonlinearities of the LNKS model.
First column: the distribution of the input light intensity and two nonlinearities. The thresholds of two nonlinearities for the On- and Off-pathways are identical. Second column: the eigenvalues of the principal component analysis. Third column: On and Off linear filters and their estimates compared with the spike-triggered average (STA). Fourth column: two clusters identified by the K-means clustering algorithm.
The nonlinearity thresholds are 1, 2, 3, and 4 from the top to bottom.

The two-pathway LN model was optimized to fit the firing rate data that was generated by the LNKS model. The two filters found from the K-means clustering were used as initial filters. I performed gradient descent based optimization algorithm where the cost function was to minimize the l_2-norm of the distance between the firing rate data and the model estimate. The overall correlation coefficient of the firing rate between the data and the two-pathway LN model was ~80%, which was significantly higher compared to ~60% computed with a single pathway LN model estimated by the STA and an instantaneous static nonlinearity. The comparison plot of the firing rates is made in the Figure 9.
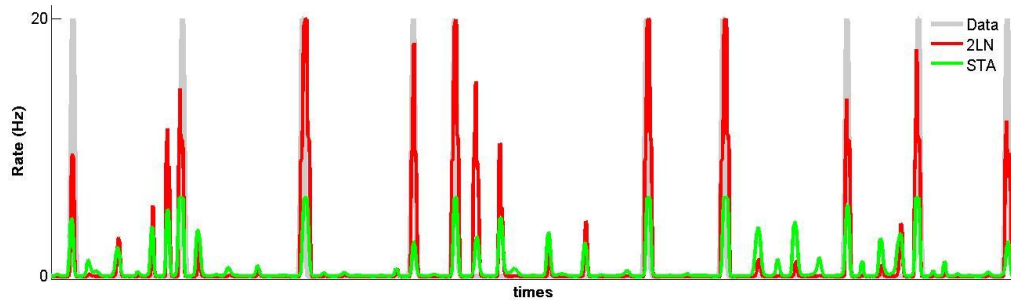

Figure 9. Comparison of a two-pathway LN model and a single pathway LN model fit to the firing rate.
Gray: the firing rate data generated using the two-pathway LNKS model as shown in Figure 4.
Red: the estimate of the firing rate using the two-pathway LN model.
Green: A single pathway LN model prediction of the firing rate. The Linear filter(L) is the STA, and the Nonlinearity(N) is an instantaneous transformation from the output of the STA and the firing rate.

4. Conclusion

To have a deeper understanding of the retinal inner circuitry, a parallel two-pathway Linear-Nonlinear(LN) model is used, where each pathway represent the average response from On-and Off-bipolar cells. In this project, I applied principal component analysis and K-means clustering algorithm to identify these two pathway linear filters. Having higher nonlinearity threshold produced a distinctive principal component which allowed me to detect two clusters. In contrast, it was difficult to classify spike-triggered ensemble using K-means algorithm when low nonlinearity threshold value was assigned. The two-pathway LN model using the two filters has more biophysical explanation, and thus fits the firing rate data more accurately compared to using just a single pathway LN model. Future work may be done to resolve the poor detection problem of two clusters for lower nonlinearity threshold.

5. Acknowledgements

6. References

Baccus, S. a. (2007). Timing and computation in inner retinal circuitry. Annual review of physiology, 69, 271–90. doi:10.1146/annurev.physiol.69.120205.124451

Chichilnisky, E. J. (2001). A simple white noise analysis of neuronal light, 12, 199–213.

Fairhall, A. L., Burlingame, C. A., Narasimhan, R., Harris, R. a, Puchalla, J. L., & Berry, M. J. (2006). Selectivity for multiple stimulus features in retinal ganglion cells. Journal of neurophysiology, 96(5), 2724–38. doi:10.1152/jn.00995.2005

Geffen, M. N., De Vries, S. E. J., & Meister, M. (2007). Retinal ganglion cells can rapidly change polarity from Off to On. PLoS biology, 5(3), e65. doi:10.1371/journal.pbio.0050065

Gollisch, T., & Meister, M. (2008). Modeling convergent ON and OFF pathways in the early visual system. Biological cybernetics, 99(4-5), 263–78. doi:10.1007/s00422-008-0252-y

Keat, J., Reinagel, P., Reid, R. C., & Meister, M. (2001). Predicting every spike: a model for the responses of visual neurons. Neuron, 30(3), 803–17.

Ozuysal, Y., & Baccus, S. a. (2012). Linking the computational structure of variance adaptation to biophysical mechanisms. Neuron, 73(5), 1002–15. doi:10.1016/j.neuron.2011.12.029