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B. Cessac, Université Côte d'Azur, INRIA, Biovision team and Neuromod Institute Sophia Antipolis, France





#### Retina's layered structure

Light



1

retinal pigment epithelium (RPE) -

#### Retina's layered structure









#### Retina's layered structure



**T THEFTER FELL CONTINUES FOR IT FOR** 

« Information » flux

#### Retina's layered structure









Source : http://webvision.med.utah.edu/





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Source: https://project.inria.fr/keops/



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*What happens if one enhances the lateral inhibition with drugs ?*

3 *genetically modified mice). Clozapine N Oxide (CNO) increases the activation level of amacrine cells (in* 

 **How does the inner retinal network shape the ganglion cells receptive field : a computational study,** E. Kartsaki, G. Hilgen, E. Sernagor, B. Cessac, Neural Computation, 2024, 36 (6).



Figure 3.1. Designer Receptor Exclusively Activated by Designer Drugs. Left. Neurotransmitters bind to G protein-coupled receptors (GPCRs) of the membrane, which leads to a change in the activity of the neuron. *Right*. An engineered version of GPCRs, called DREADDs, responds only to a specific biologically inert chemical (a designer drug), hence allowing us to control neuronal activity. Source: https://benchling.com/pub/dreadds

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DREADDs can be excitatory (hM3Dq - release of calcium from organelles leading to increase of intracellular concentration of free calcium, leading to membrane depolarisation and higher neuronal excitability), or inhibitory (hM4Di - opening of potassium channels, leading to membrane hyperpolarisation and neuronal silencing).

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Bipolar voltage:

$$
\frac{dV_{B_i}}{dt} = -\frac{1}{\tau_{B_i}} V_{B_i} + \sum_{j=1}^{N_A} W_{B_i}^{A_j} \mathcal{N}^{(A)}(V_{A_j}) + F_{B_i}(t)
$$

External drive:  $\bullet$ 

Gain control

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$$
F_{B_i}(t) = \frac{\mathscr{V}_i^{(drive)}}{\tau_{B_i}} + \frac{d}{dt} \mathscr{V}_i^{(drive)}.
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Amacrine voltage :  $\bullet$ 

$$
\begin{array}{lll} \frac{dV_{A_j}}{dt} & = & -\frac{1}{\tau_{A_j}}V_{A_j} + \sum_{i=1}^{N_B} W_{A_j}^{B_i} \mathcal{N}^{(B)}\left(V_{B_i}\right) + \zeta_A \end{array}
$$

- Coupled dynamics:  $\bullet$
- $\frac{dV_{B_i}}{dt}$  =  $-\frac{1}{4g_i}V_{B_i} + \sum_{j=1}^{N_A} W_{B_i}^{A_j} \mathcal{N}^{(A)}(V_{A_j}) + F_{B_i}(t), i = 1...N$  $\frac{dV_{A_j}}{dt} = -\frac{1}{\tau_{A_j}}V_{A_j} + \sum_{i=1}^{N_B} W_{A_j}^{B_i} \mathcal{N}^{(B)}(V_{B_i}) + \zeta_A, \quad j = 1...N,$  $\frac{dV_{G_k}}{dt} = -\frac{1}{\tau_{G_k}} V_{G_k} + \sum_{i=1}^{N_B} W_{G_k}^{B_i} \mathcal{N}_B(V_{B_i}) + \sum_{j=1}^{N_A} W_{G_k}^{A_j} \mathcal{N}_A(V_{A_j}) + \zeta_G, \quad k = 1...N.$

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 **How specific classes of retinal cells contribute to vision : a computational model,** Evgenia Kartsaki, PhD, 2022



Potential scenarios of DREADD activation. 1. ACs and RGCs do not express Figure 3.7. DREADDs, thus there is no change in the spiking activity of the RGCs. 2. Only RGCs express DREADDs, so DREADD activation is triggering increased RGC firing. 3. Only ACs express DREADDs, so DREADD activation causes an increase of the putatitve inhibitory effect of ACs on RGCs, resulting in decreased RGC firing. 4. Both ACs and RGCs express DREADDs, therefore DREADD activation triggers an excitatory direct effect on RGCs and an inhibitory indirect effect via ACs on RGCs. The net effect is not clear on experimental grounds. Figure Courtesy Dr. Hilgen.










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#### Control condition

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**CNO** 

 $f(\boldsymbol{\omega})$ : Meromorphic function in the complex plane



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From resonances to monophasic profile



From resonances to polyphasic profile





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Application of CNO (Clozapine N Oxide)



 $t$  (ms)



0.0 120.0 240.0 360.0 480.0 600.0  $t$  (ms)

 $-0.2$ 











#### **Conjecture :**

A moving object triggers **waves of activity** in the retina (and in the visual cortex).

These waves are shaped and modulated by **lateral inhibition**.

The conjunction of the moving stimulus and of the forward/ backward and excitatory/inhibitory effects **selects** spatial wave lengths and temporal frequencies leading to **specific responses** and **resonance effects**.









$$
f(k) = \frac{1}{k - k^*}
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$$









$$
f(\boldsymbol{\omega}) = \frac{1}{\boldsymbol{\omega} - \boldsymbol{\omega}^*} \qquad \qquad \sum_{\mathbf{S} \sim \mathbf{I} \mathbf{O}^{12}} \widehat{\mathbf{O}^*}
$$















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- Each pole is characterized by four numbers **(kr,ki,ωr,ωi)** that can be extracted from the power spectrum *provided the resolution is large enough*.



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- The location of the poles in the complex space give rise to **different type of dynamical responses.**

### Lateral inhibition can induce retinal anticipation



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# Lateral inhibition can induce retinal anticipation

Adapted from M. Menz et al., bioRxiv (2020)















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- The location of the poles in the complex space give rise to **different type of dynamical responses.**

# How does lateral inhibition shape the response to moving stimuli ?



A moving object triggers **waves of activity** in the retina .

### These waves are shaped and modulated by **lateral inhibition**.

The conjunction of the moving stimulus and of the forward/ backward and excitatory/inhibitory effects **selects** spatial wave lengths and temporal frequencies leading to **specific responses** and **resonance effects**.

These effects are characterized by **poles** in the complex plane, appearing in the **spatiotemporal Fourier transform**.

## **ESTHETICS/FUSION Projects**

*Exploring the functional structure of the retina with closed loop Stimulation. A physiological and computational approach* 

> **Centro de Neurociencia de Valparaiso, Chile Universitad Santa-Maria, Valparaiso, Chile**

> > **MacTao team, Inria I3S, CNRS, Université Côte d'Azur**

> > > **Biovision team, Inria**



#### $(C)$

Recording start

Recording end



Pulse amplitude  $(\mu A)$ 

Photoreceptors



Photoreceptors



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- Too complex a structure (natural movies).
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### **Context**

*Develop a new strategy, combining experiments and modeling, to better understand the retinal network dynamics using appropriate spatiotemporal stimuli and closed loop experiments.*

**Fundings** : RISE, DocWalker, Associated INRIA Team Fusion, EDSTIC



#### **1 Stay of S. Ebert in Valparaiso (DocWalker, Oct.-Nov. 2023) :**

- Design of simple stimuli;
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#### **2 Venue of F. Miqueles and J. Portal-Diaz at INRIA (Esthetics, Feb.-Apr. 2024):**

- Tools to analyse the spatio temporal information provided by raw data;
- Spatio temporal FFT, attempts to characterize a convolution kernel;
- Spikes in ERG;
- Parameters estimation + stimulus design.





Zapp, Sören J. et al. Trends in Neurosciences, Volume 45, Issue 6, 430 - 445

The behaviour of individual retinal cells is characterized by a cascade of convolutions and weak non linearities.



- S. Souihel, B. Cessac, Journal of Mathematical Neuroscience, 2021, 11
- B. Cessac, Journal of Imaging, 2022, 8 (1)
- E. Kartsaki, G. Hilgen, E. Sernagor, B. Cessac, Neural Computation, 2024, 36 (6)
- S. Ebert, T. Buffet, B. S. Sermet, O. Marre, B. Cessac, Nature Com., 2024, 15 (6118)

The behaviour of the **retinal network** is characterized by a cascade of convolutions and weak non linearities.



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$$
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#### **1 Modelling the retinal response to moving stimuli (S. Ebert, L. Piovano)**

- Explicit computation of a spatio-temporal kernel featuring the retina response
- Property of the Fourier Transform
- Existence of spatio-temporal **resonances**.



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#### **2 E. Petit thesis (funding EDSTIC)**

- Parameters estimation from experiments in a simplified retina model
- Simulations on the Macular simulator.

**Retinal Network Response MEA, ERG**



### **Virtual network**

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### **3 Mathematical study of optimal design (L. Sacchelli, INRIA - L. Pronzatto, I3S)**

- Exploring different criteria for optimal design (KL divergence, information)
- ANR project lead by L. Sacchelli





### **1 Stay of E. Petit, B. Cessac in Valparaiso (January 2025)**

- Attending the *Laconeu Sumer School*.
- Attend experiments, learn how to handle data, how to efficiently interact given the distance.
- Discuss the problem of *MEA resolution*
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## **Bibliography**

1. « *Closed loop strategy to characterize the retinal network: preliminary steps* », B. Cessac, S. Ebert, M.J. Escobar, F. Miqueles, A. Palacios, E. Petit, J. Portal-Diaz, Inria research report. In progress.

2. « *Parameters estimation in a retinal network model* », B. Cessac, L. Pronzato, L. Sacchelli. In progress.

3. « *On the retinal response to a moving bar* », B. Cessac, S. Ebert, L. Piovano, In progress.

4. «*Temporal refinement of spatiotemporal pattern prediction via short-term plasticity*», B. Cessac, S. Ebert, In progress.

### Conclusions

● Visual entries are **neither stationary**, nor **spatially regular**.

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- On the basis of biophysical modelling  $+$  mathematical analysis we found that Amacrine cells may generate, from a **moving stimulus**, **spatio-temporal correlations** (**waves**) contributing to better encoding a visual scene (e.g. **anticipation**).
## **Conclusions**

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## *Waves could be the fundamental key to understand the visual processing.*

*How does the brain efficiently decode a flux of spikes with multi scale spatiotemporal correlations ?*

> 1 1

## Thanks