

Bruno Cessac

► To cite this version:

Bruno Cessac. How does lateral inhibition shape the response to moving stimuli?. Latin Americal Summer School in Computational Neuroscience (LACONEU), Valparaiso, Chile, Jan 2025, Valparaiso (Chile), Chile. hal-04920942

HAL Id: hal-04920942 https://inria.hal.science/hal-04920942v1

Submitted on 30 Jan 2025 $\,$

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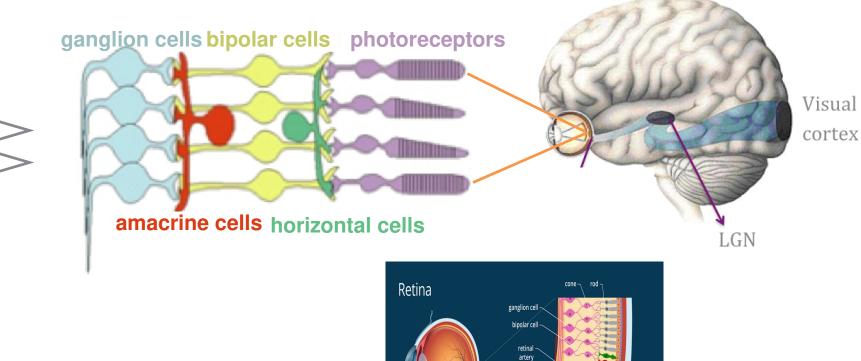
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B. Cessac, Université Côte d'Azur, INRIA,
 Biovision team and Neuromod Institute
 Sophia Antipolis, France





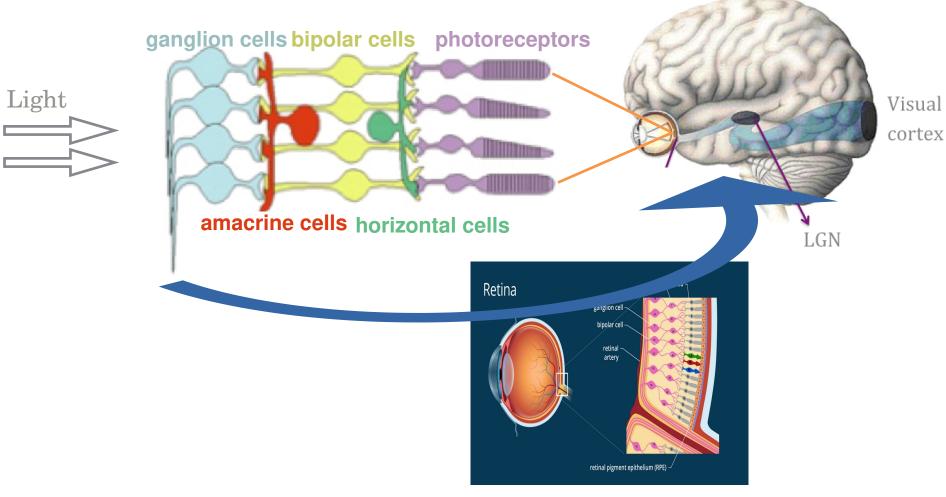
Retina's layered structure

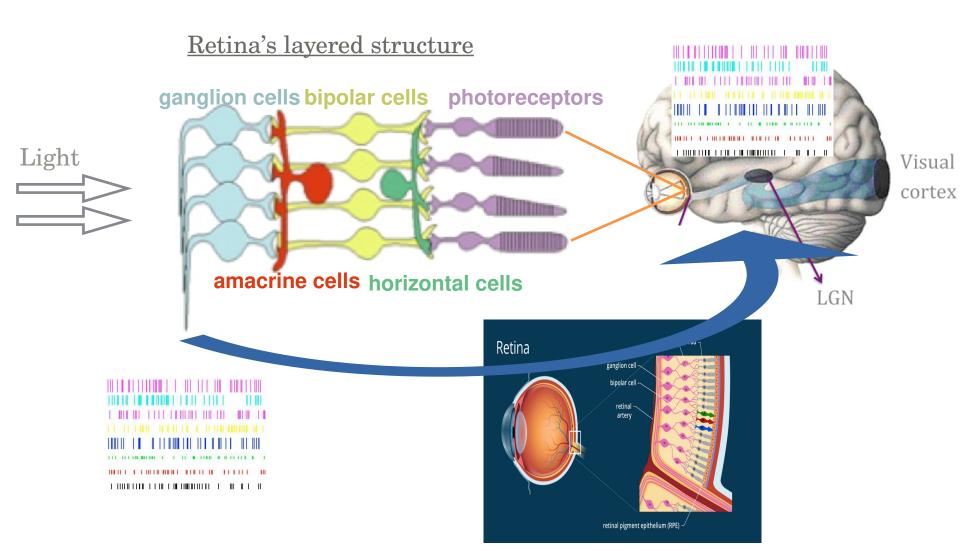


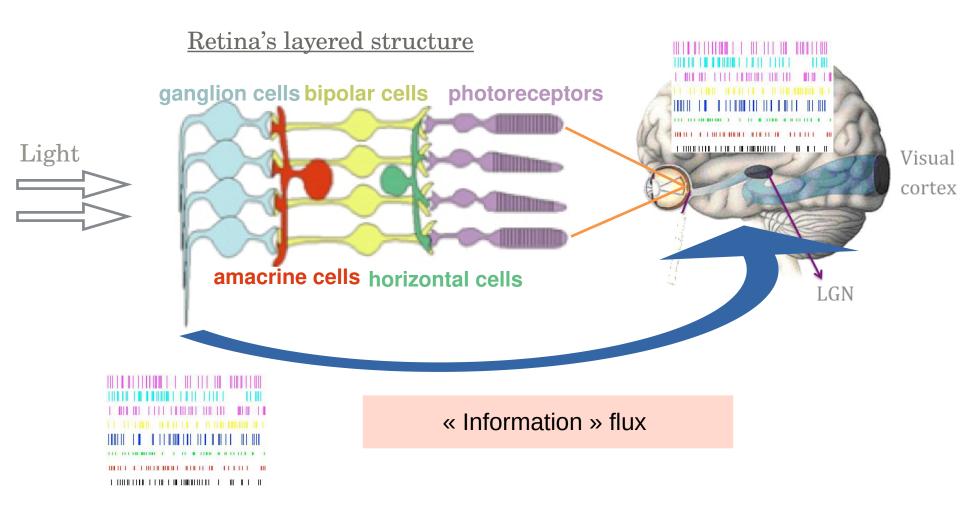
retinal pigment epithelium (RPE) -

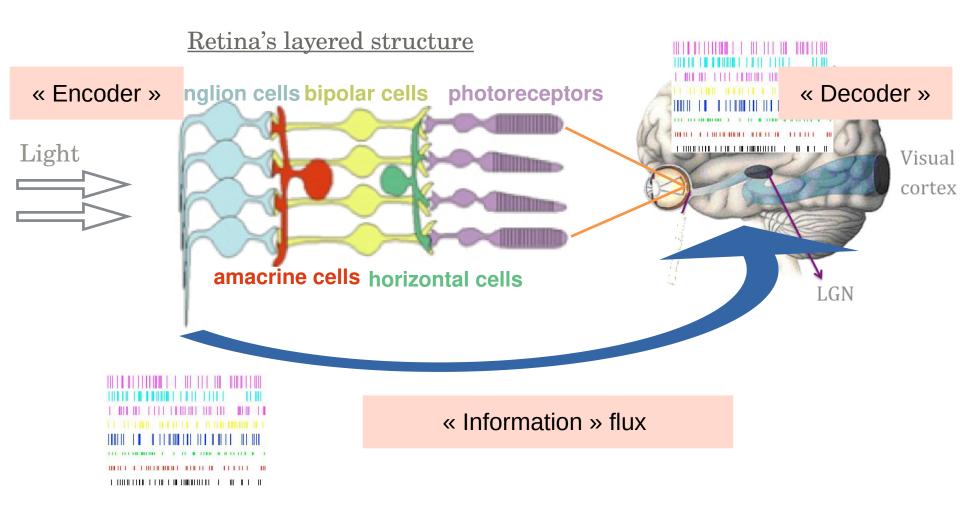
Light

Retina's layered structure



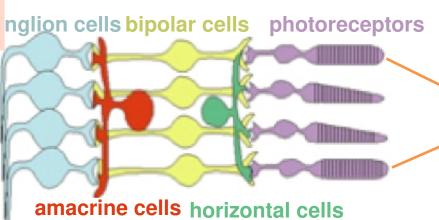






Retina's layered structure

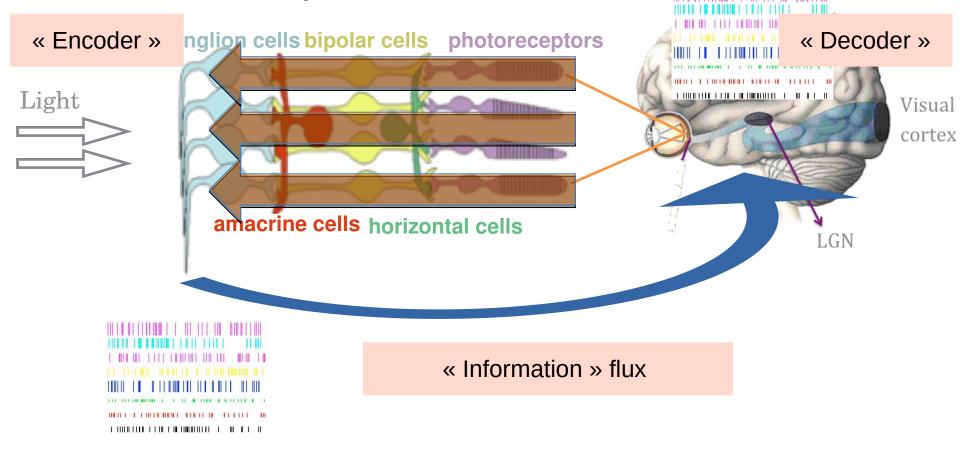


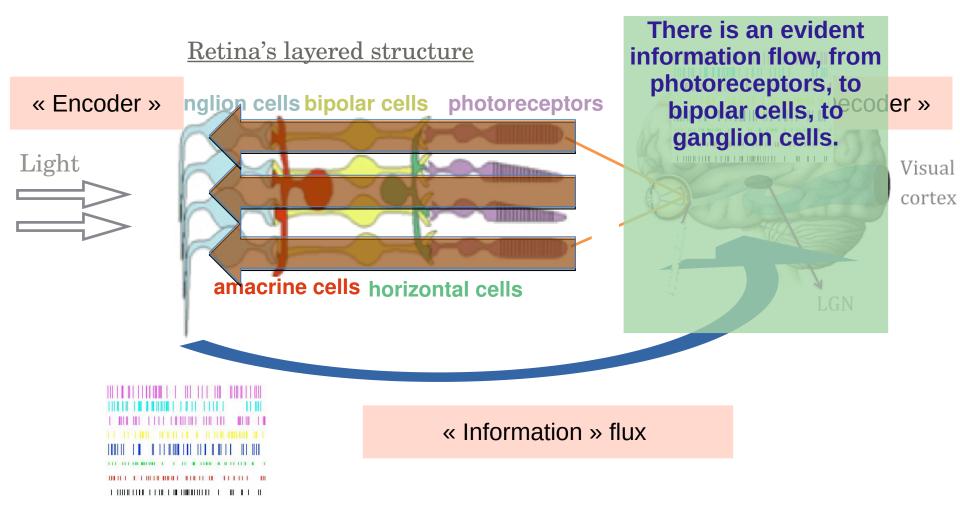


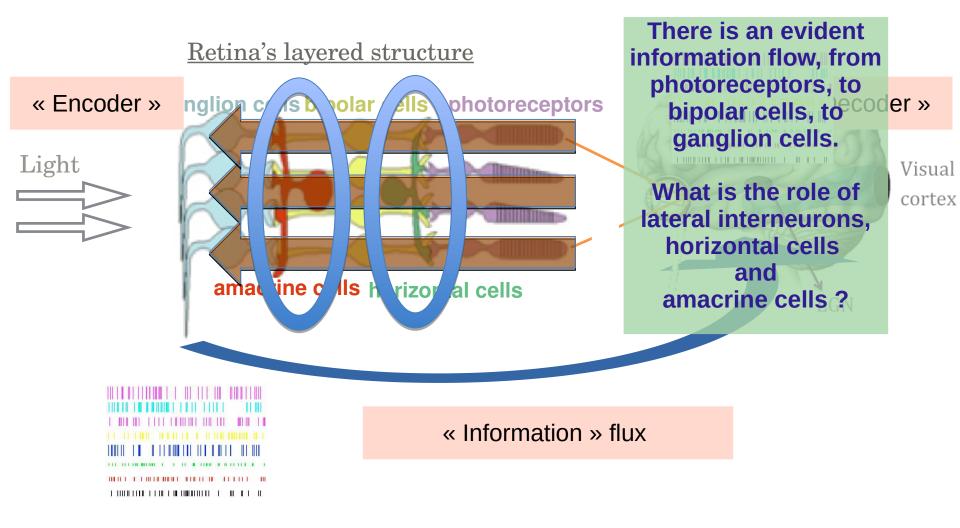


« Information » flux

Retina's layered structure

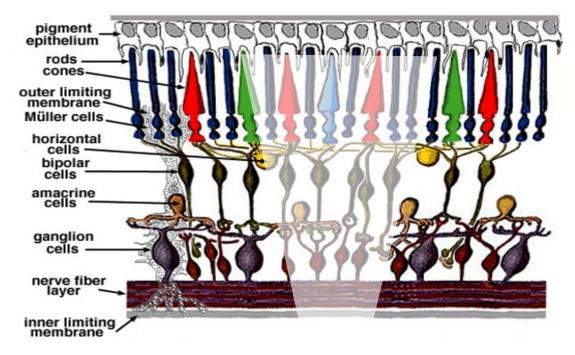






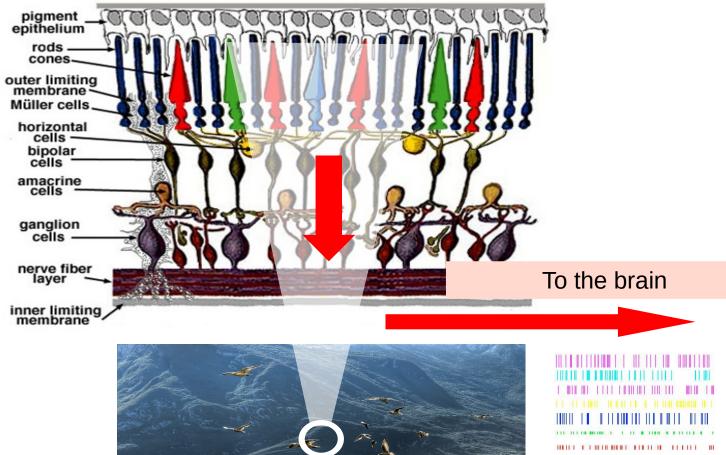


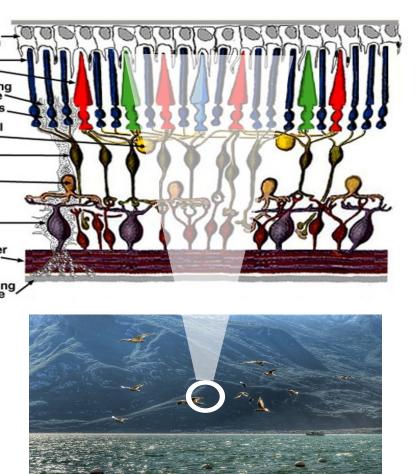
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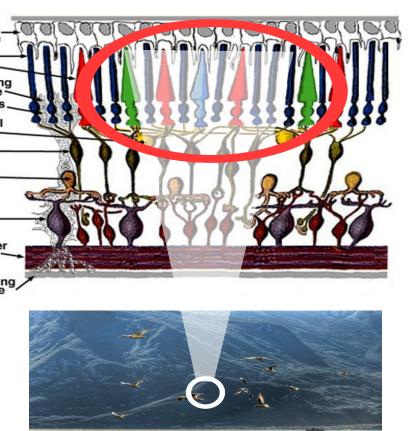


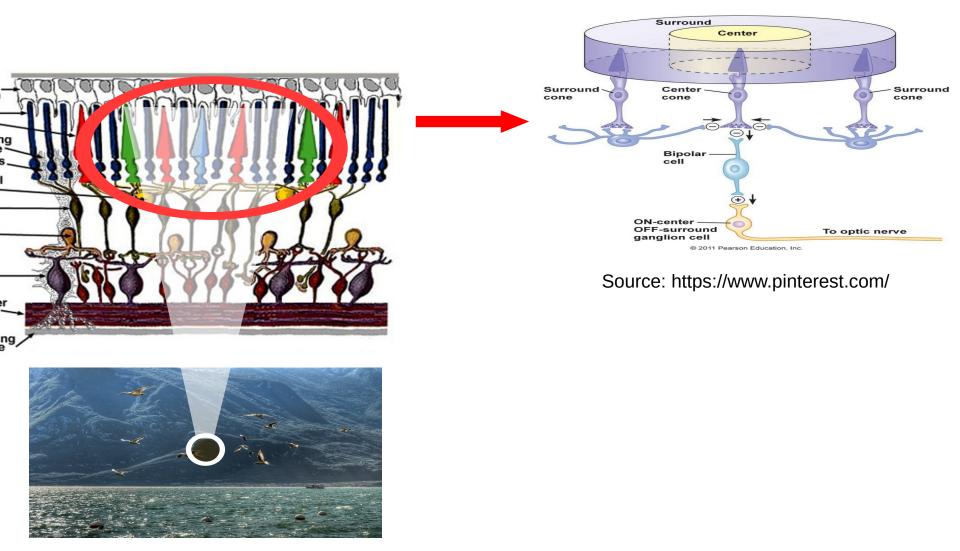


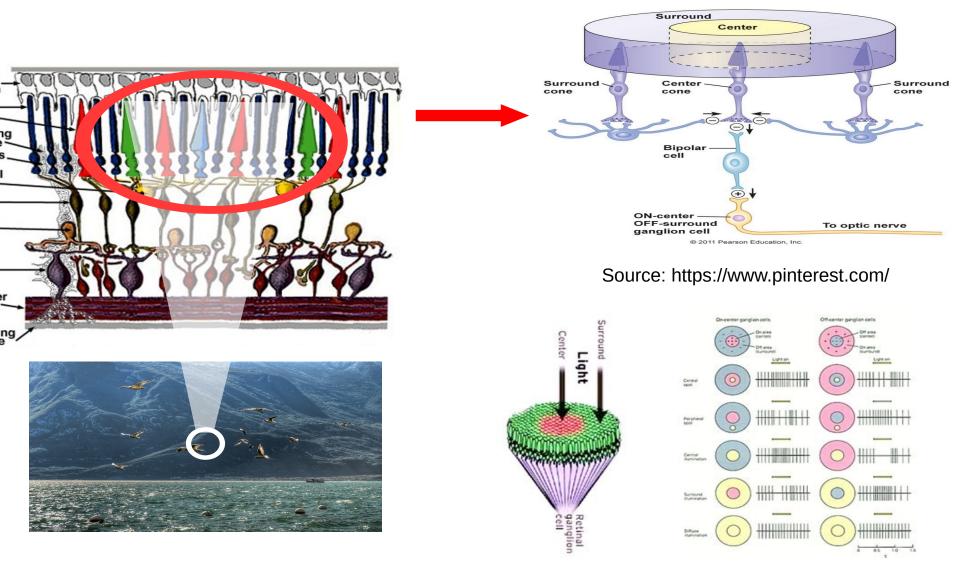
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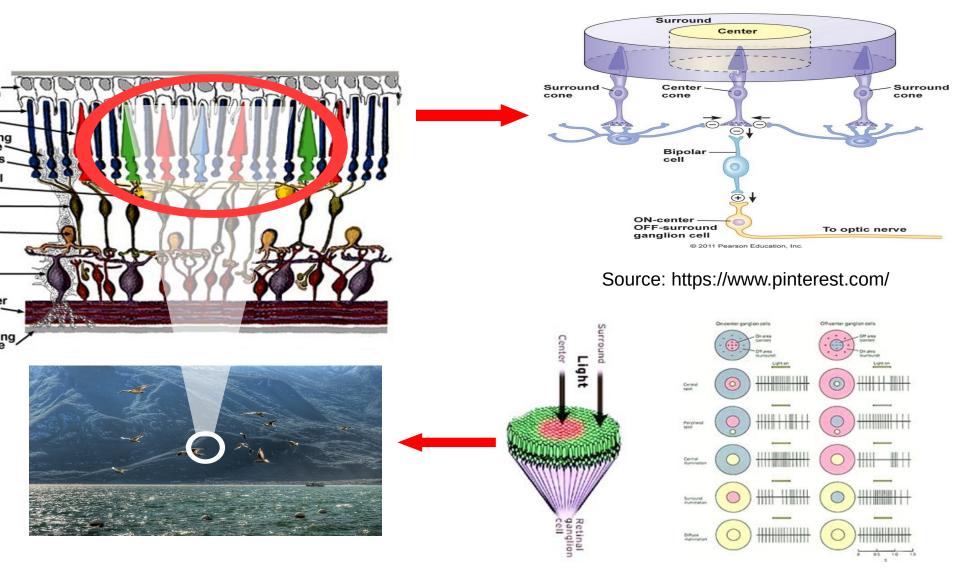




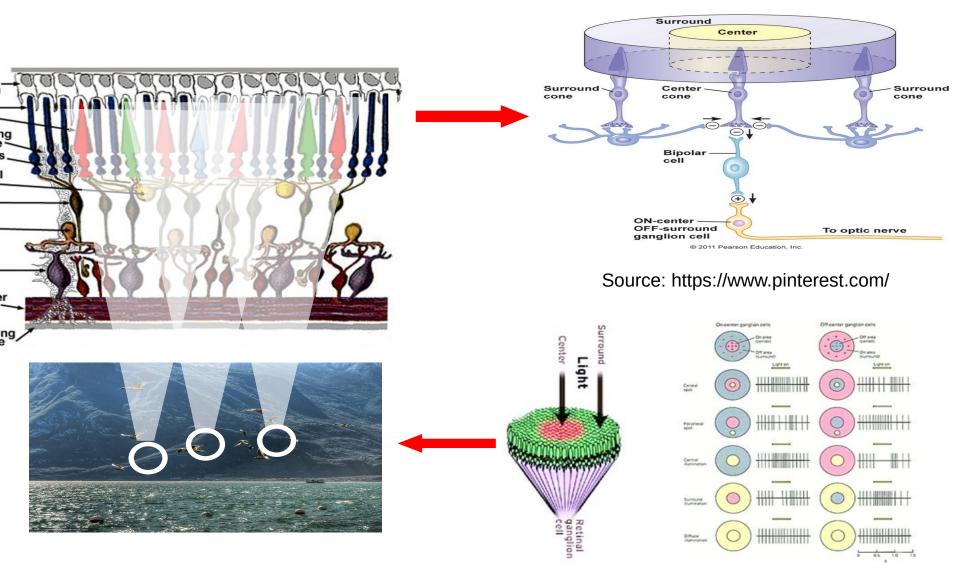




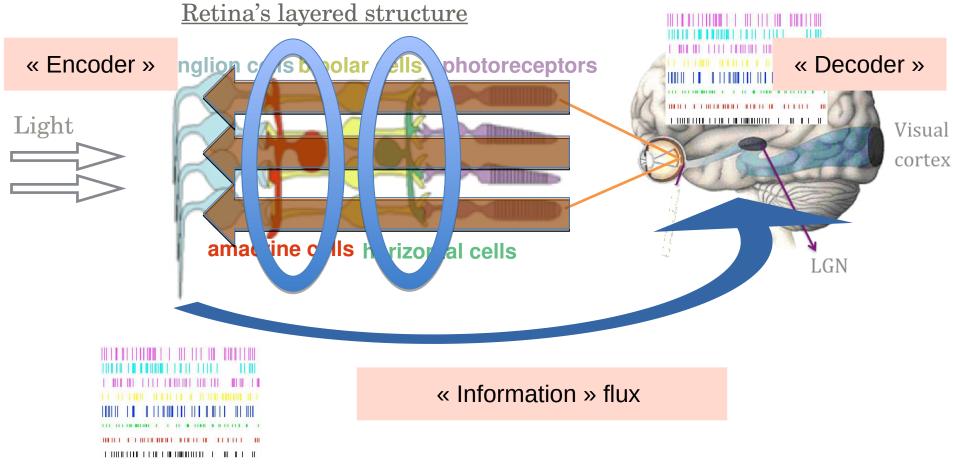
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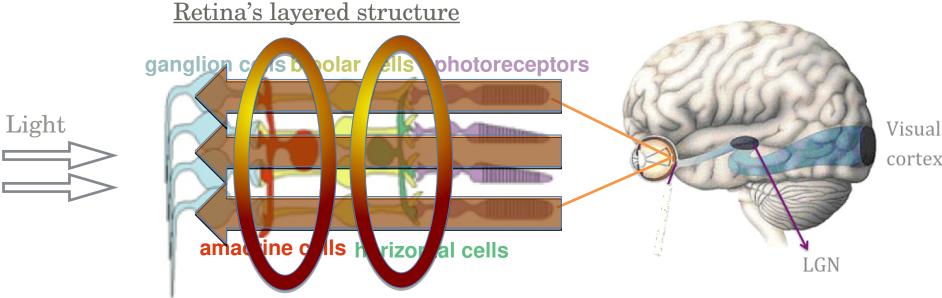


Source: https://project.inria.fr/keops/



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





cortex

What happens if one enhances the lateral inhibition with drugs?

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

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).

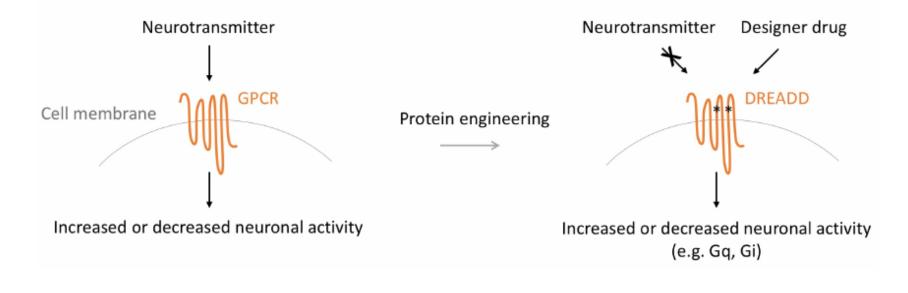
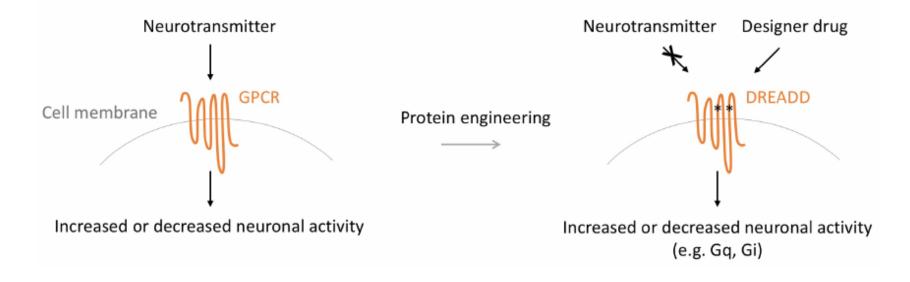


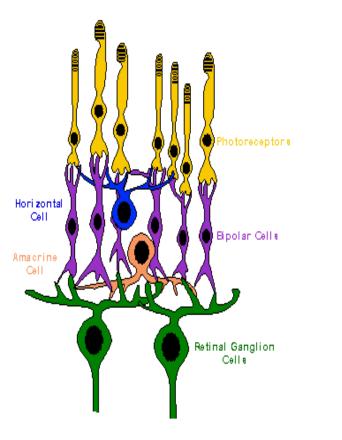
Figure 3.1. Designer Receptor Exclusively Activated by Designer Drugs. *Left*. Neurotransmitters bind to G protein-coupled receptors (GPCRs) of the membrane, which leads to a change in the activity of the neuron. *Right*. An engineered version of GPCRs, called DREADDs, responds only to a specific biologically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

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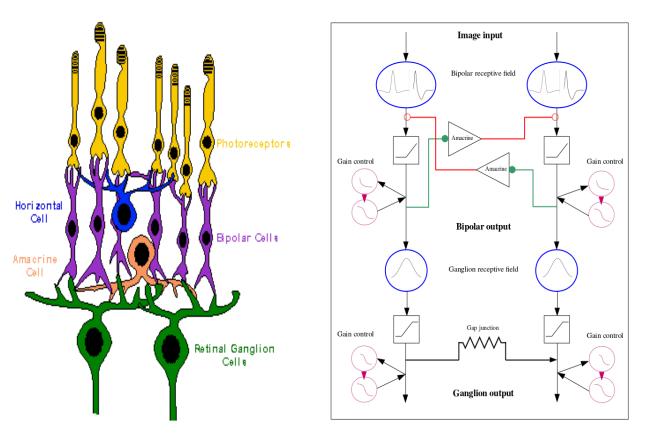


DREADDs can be excitatory (hM3Dq - release of calcium from organelles leading to increase of intracellular concentration of free calcium, leading to membrane depolarisation and higher neuronal excitability), or inhibitory (hM4Di - opening of potassium channels, leading to membrane hyperpolarisation and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

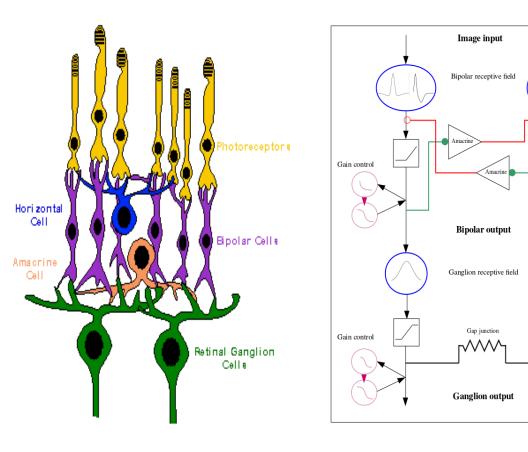
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• Bipolar voltage :

$$\frac{dV_{B_{i}}}{dt} = -\frac{1}{\tau_{B_{i}}}V_{B_{i}} + \sum_{j=1}^{N_{A}} W_{B_{i}}^{A_{j}} \mathcal{N}^{(A)}(V_{A_{j}}) + F_{B_{i}}(t)$$

• External drive :

Gain control

Gain control

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

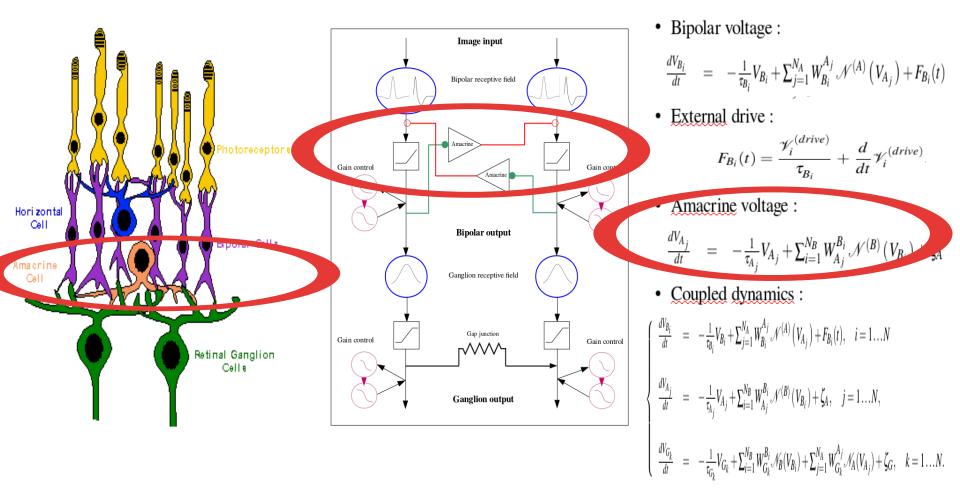
• Amacrine voltage :

$$\frac{dV_{A_{j}}}{dt} = -\frac{1}{\tau_{A_{j}}}V_{A_{j}} + \sum_{i=1}^{N_{B}} W_{A_{j}}^{B_{i}} \mathcal{N}^{(B)}(V_{B_{i}}) + \zeta_{A}$$

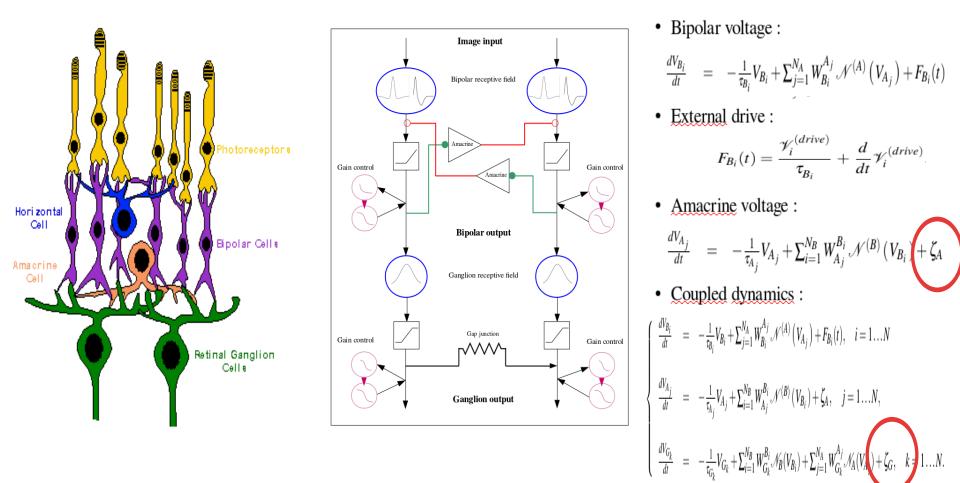
• Coupled dynamics :

$$\begin{cases} \frac{dV_{B_i}}{dt} &= -\frac{1}{\tau_{B_i}} V_{B_i} + \sum_{j=1}^{N_A} W_{B_i}^{A_j} \mathcal{N}^{(A)} \left(V_{A_j} \right) + F_{B_i}(t), \quad i = 1...N \\ \\ \frac{dV_{A_j}}{dt} &= -\frac{1}{\tau_{A_j}} V_{A_j} + \sum_{i=1}^{N_B} W_{A_j}^{B_i} \mathcal{N}^{(B)} \left(V_{B_i} \right) + \zeta_A, \quad j = 1...N, \\ \\ \frac{dV_{G_k}}{dt} &= -\frac{1}{\tau_{G_k}} V_{G_k} + \sum_{i=1}^{N_B} W_{G_k}^{B_i} \mathcal{N}_B \left(V_{B_i} \right) + \sum_{j=1}^{N_A} W_{G_k}^{A_j} \mathcal{N}_A \left(V_{A_j} \right) + \zeta_G, \quad k = 1...N \end{cases}$$

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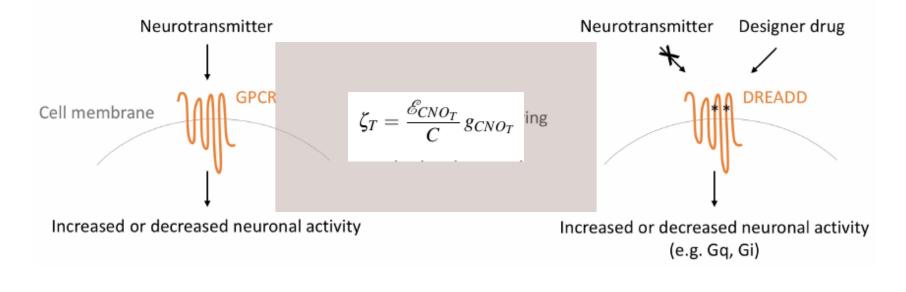
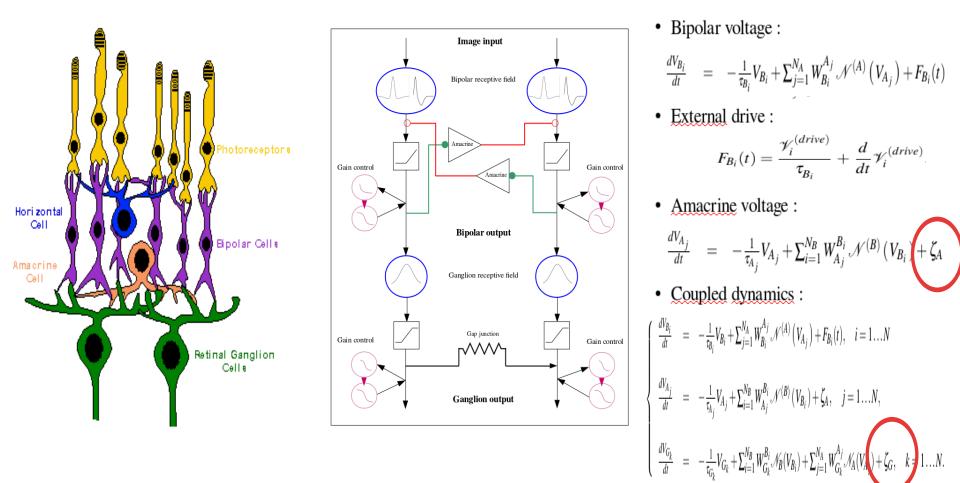


Figure 3.1. Designer Receptor Exclusively Activated by Designer Drugs. *Left*. Neurotransmitters bind to G protein-coupled receptors (GPCRs) of the membrane, which leads to a change in the activity of the neuron. *Right*. An engineered version of GPCRs, called DREADDs, responds only to a specific biologically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

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

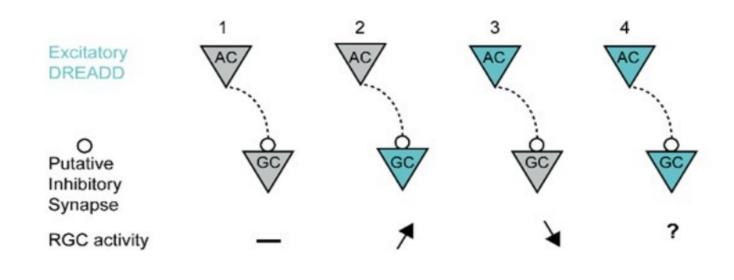
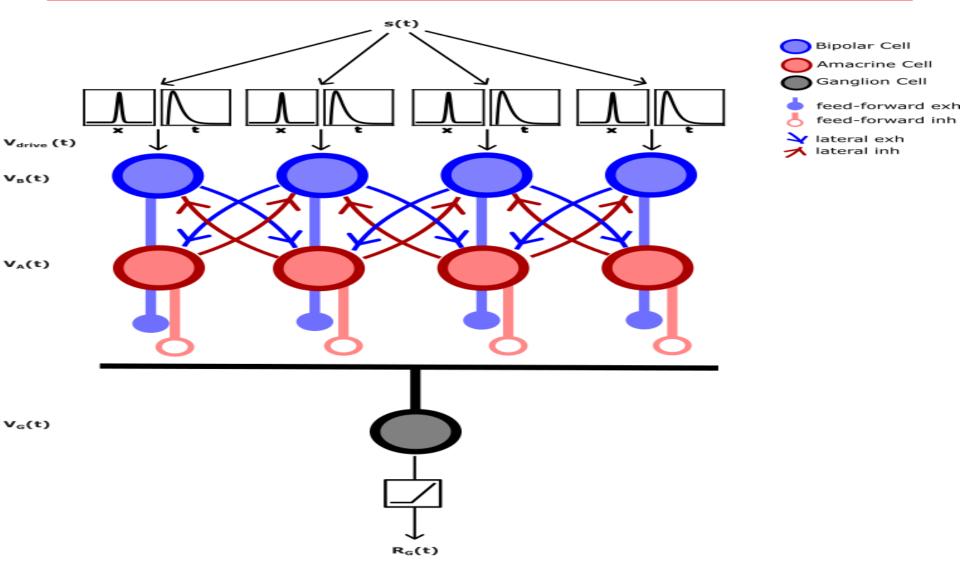
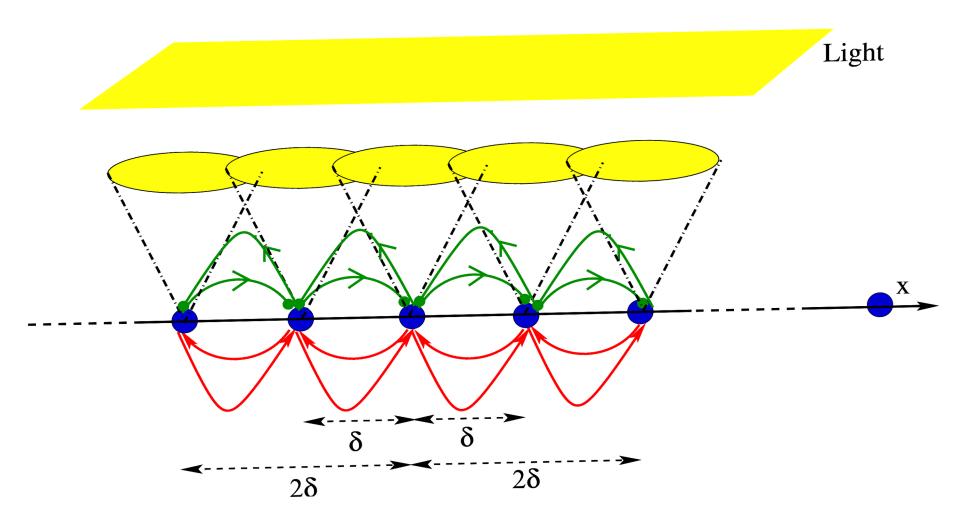
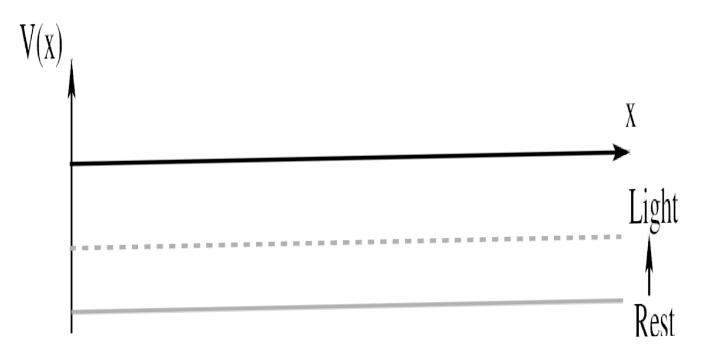
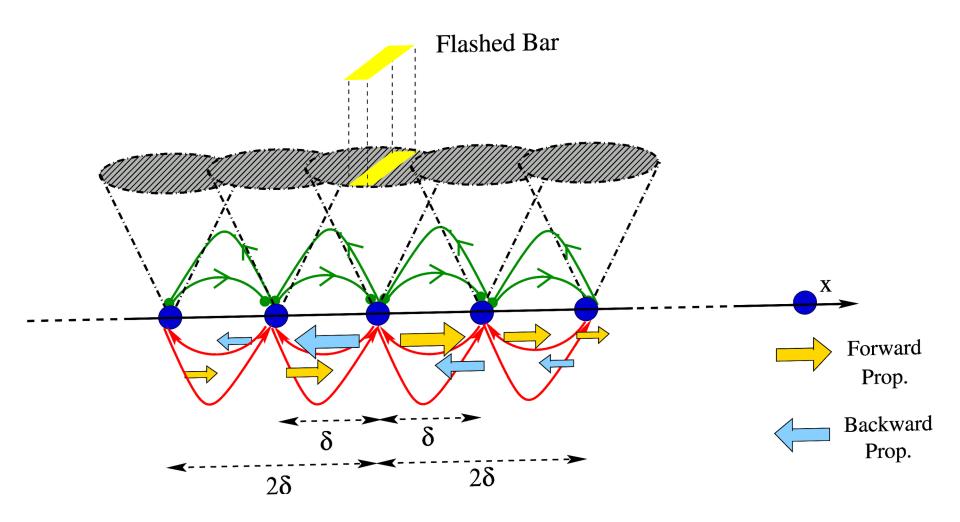


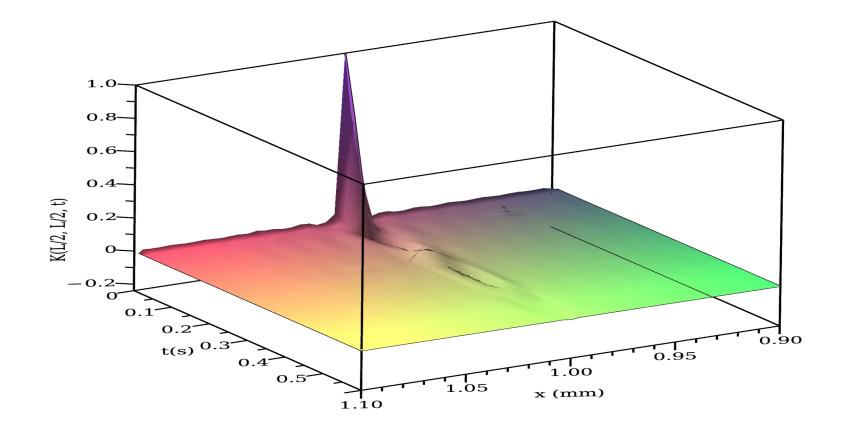
Figure 3.7. Potential scenarios of DREADD activation. 1. ACs and RGCs do not express DREADDs, thus there is no change in the spiking activity of the RGCs. 2. Only RGCs express DREADDs, so DREADD activation is triggering increased RGC firing. 3. Only ACs express DREADDs, so DREADD activation causes an increase of the putative 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.



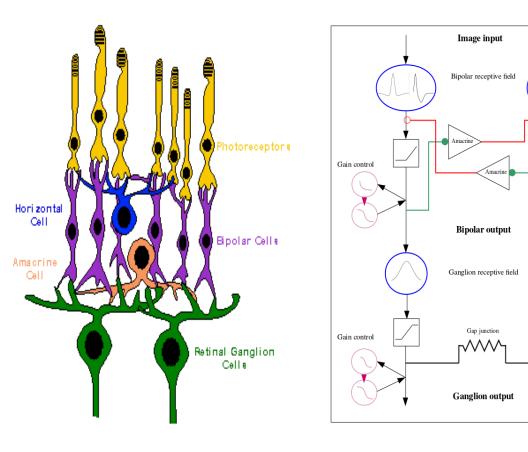








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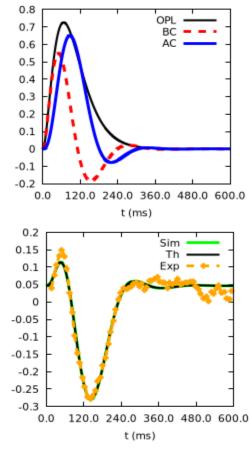
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• Coupled dynamics :

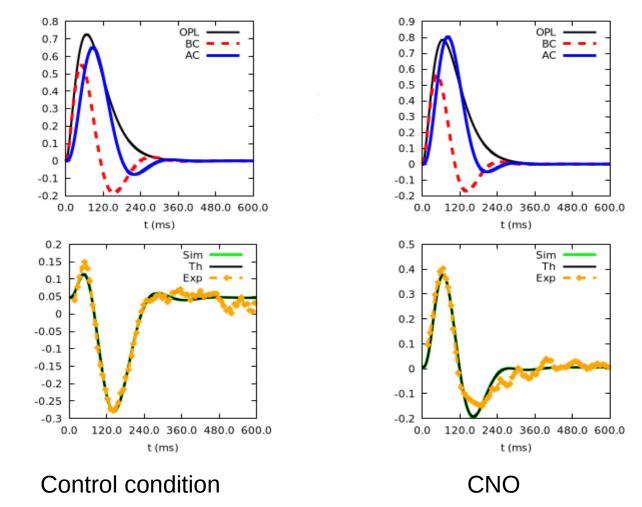
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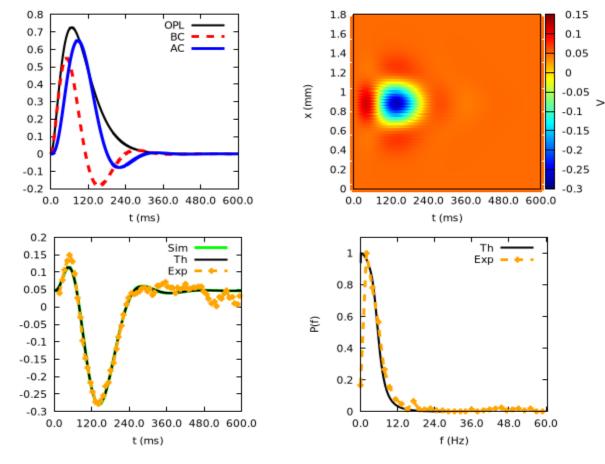


Control condition

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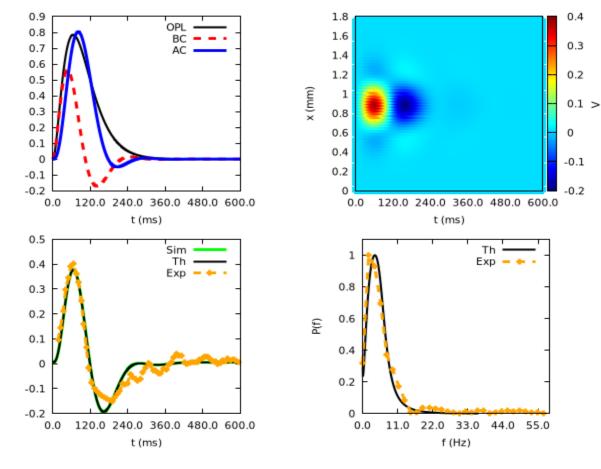


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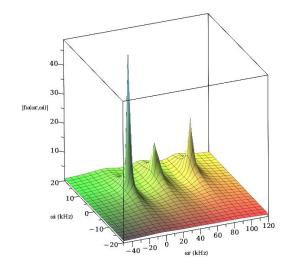
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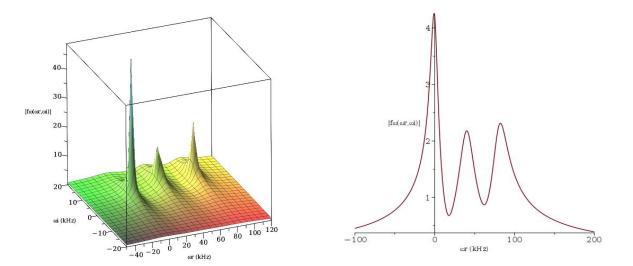


CNO

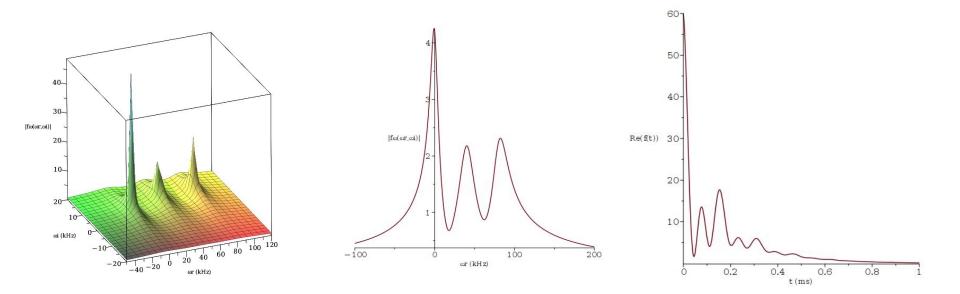
 $f(\pmb{\omega})$: Meromorphic function in the complex plane



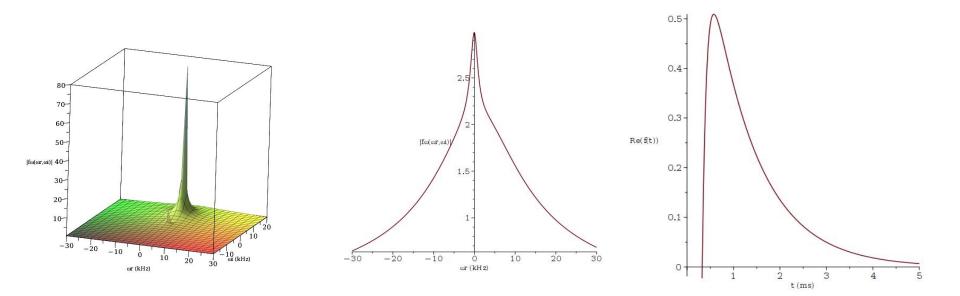
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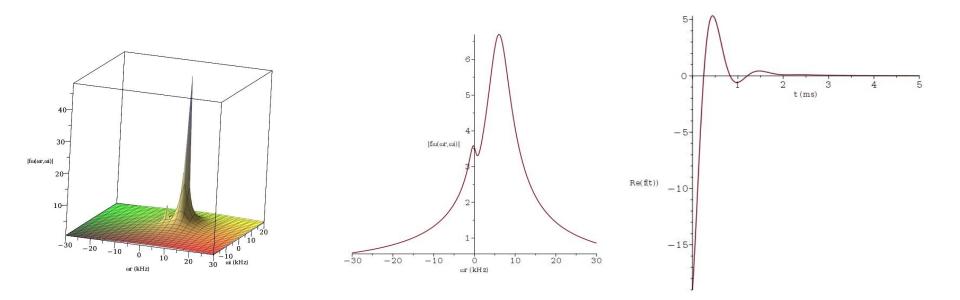
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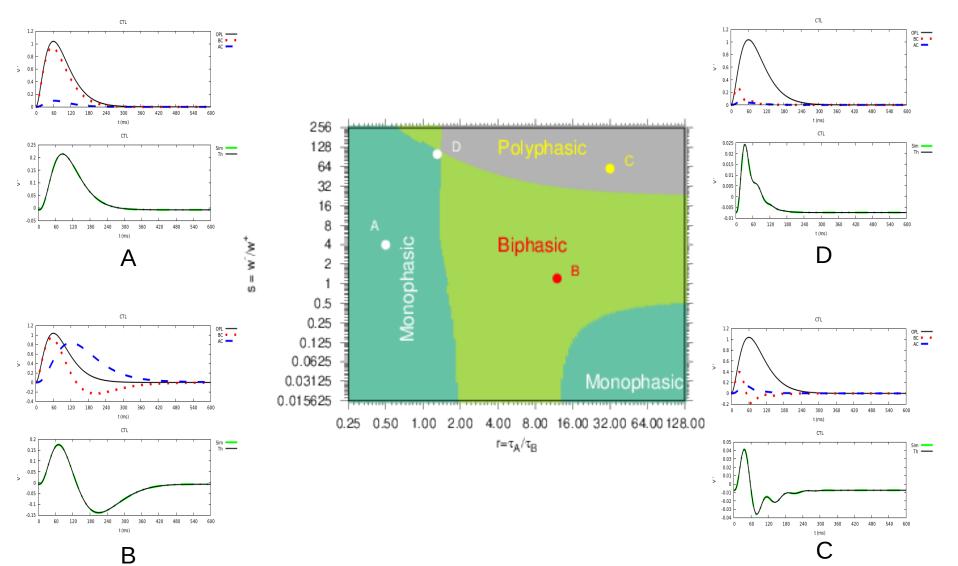


From resonances to monophasic profile

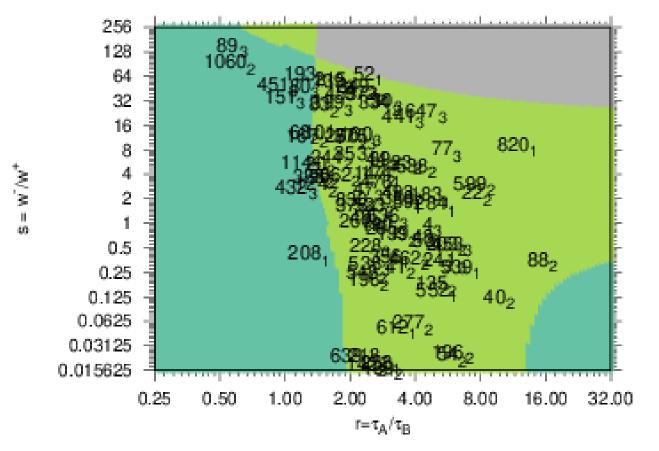


From resonances to polyphasic profile



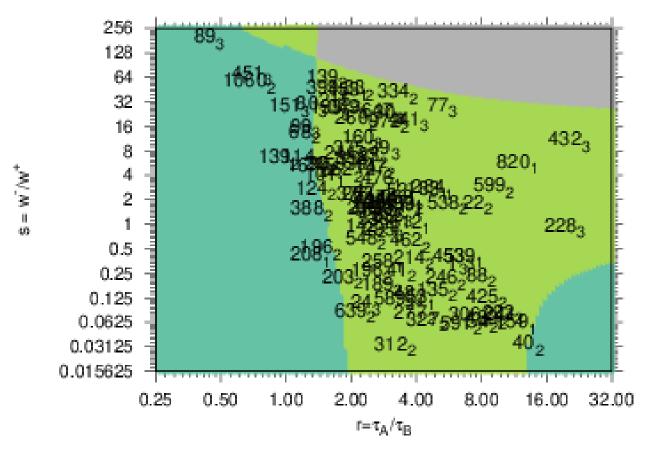


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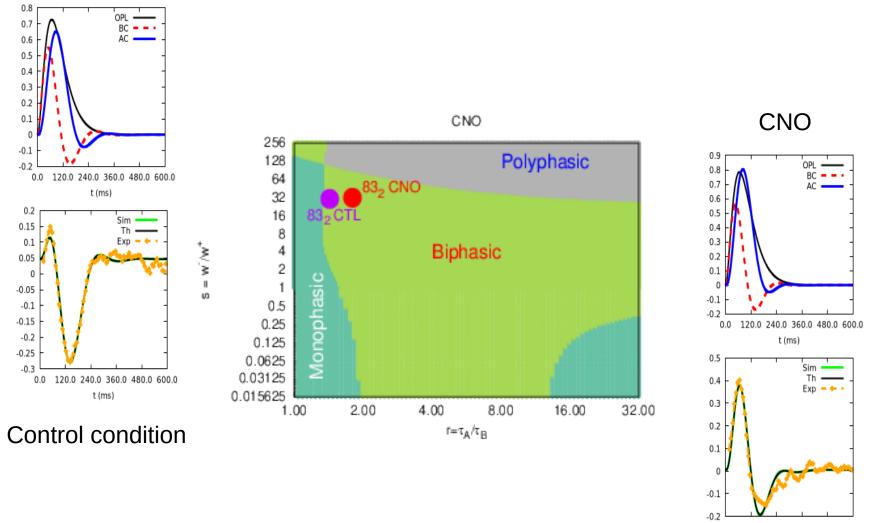


Control condition

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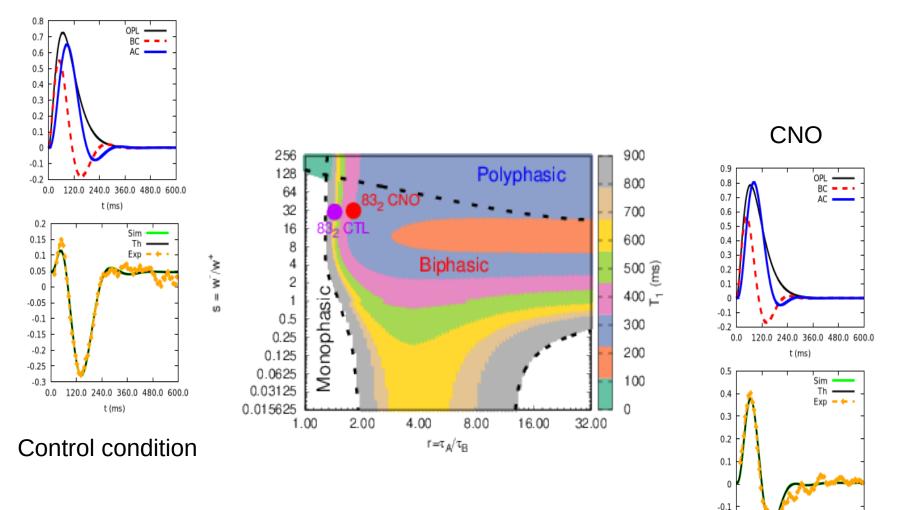


Application of CNO (Clozapine N Oxide)



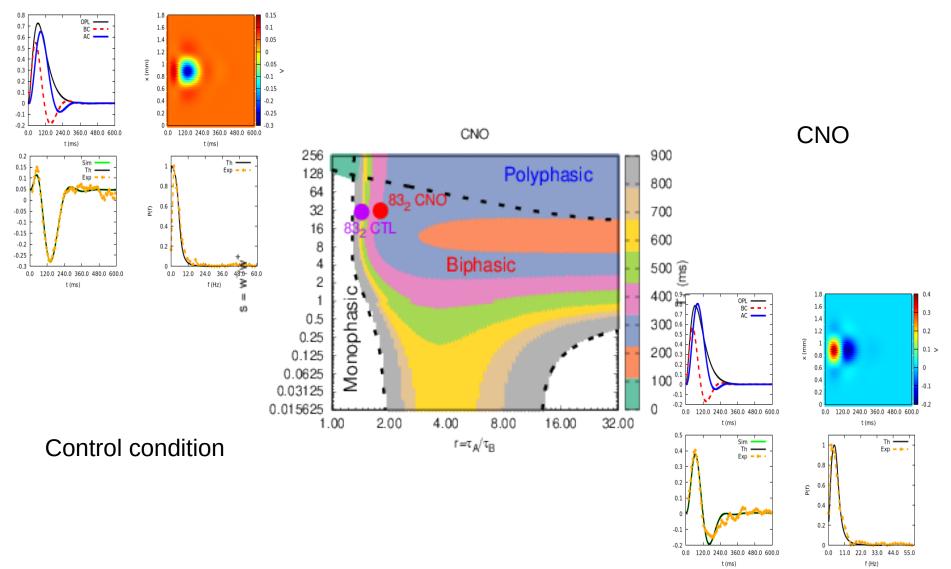
0.0 120.0 240.0 360.0 480.0 600.0

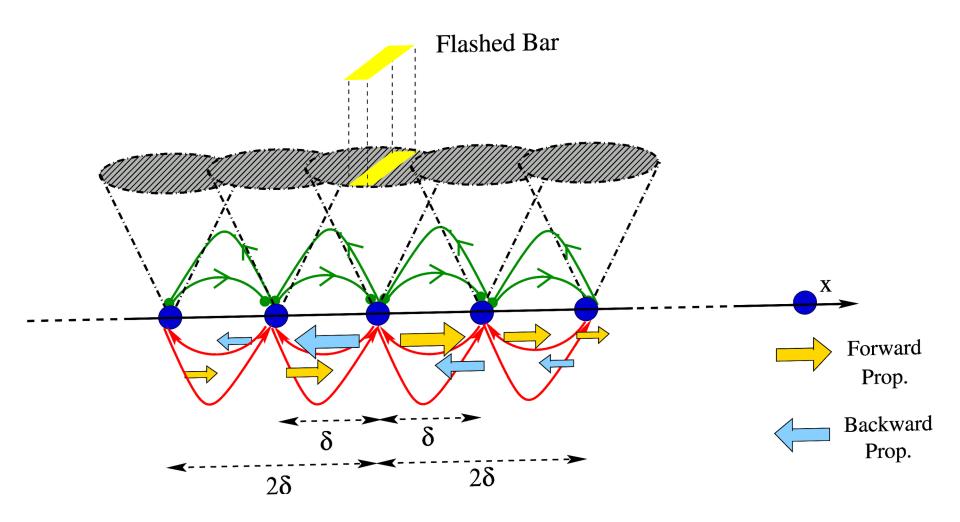
t (ms)

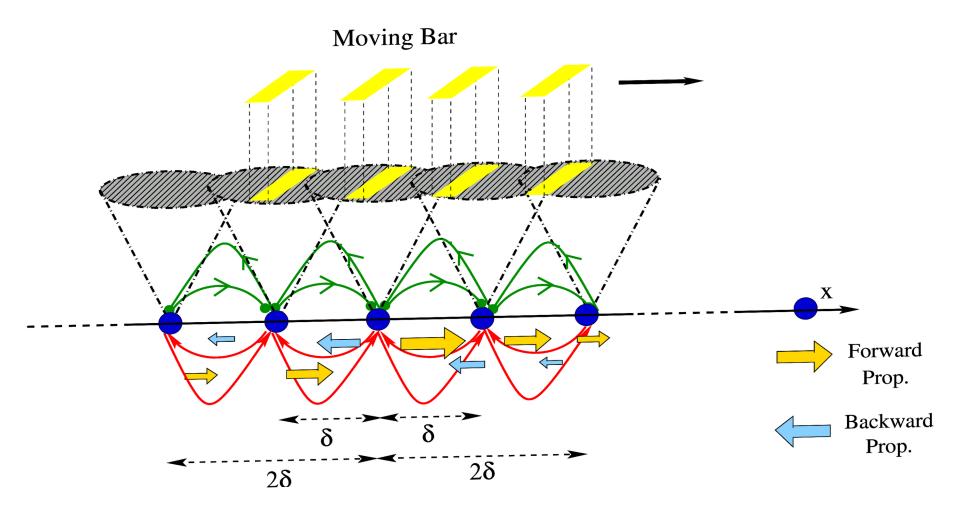


0.0 120.0 240.0 360.0 480.0 600.0 t (ms)

-0.2









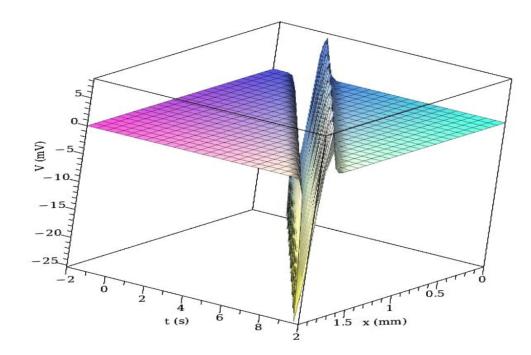


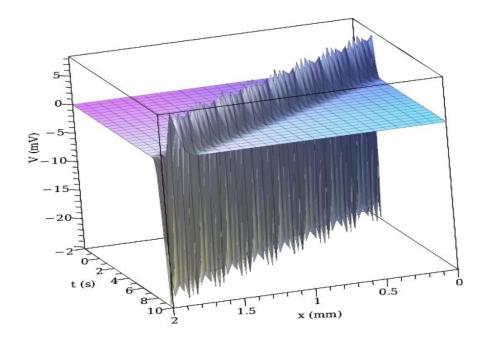
Conjecture :

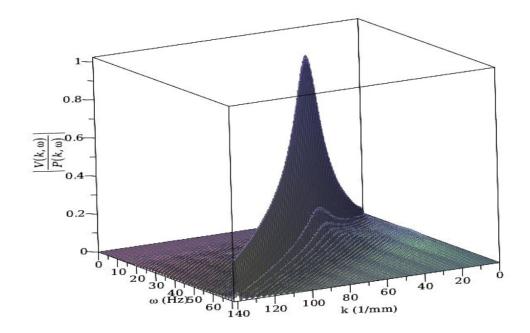
A moving object triggers waves of activity in the retina (and in the visual cortex).

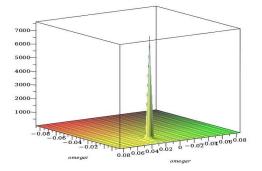
These waves are shaped and modulated by lateral inhibition.

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**.

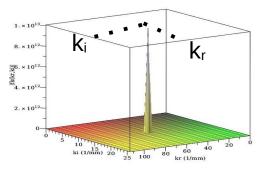




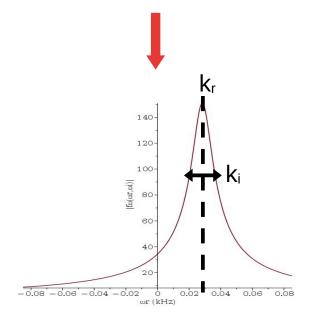


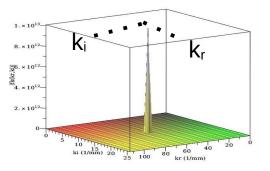


$$f(k) = \frac{1}{k - k^*}$$

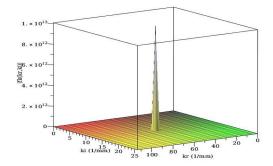


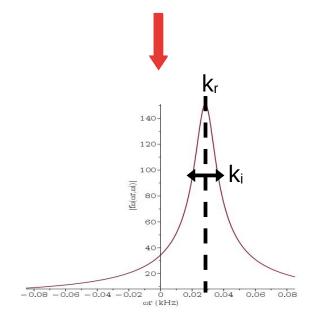
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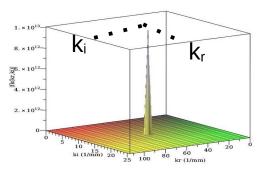


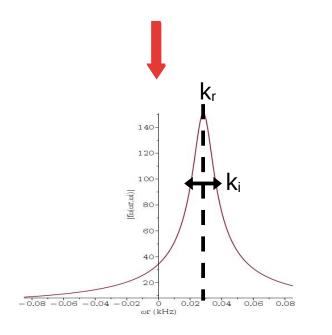


$$f(\boldsymbol{\omega}) = \frac{1}{\boldsymbol{\omega} - \boldsymbol{\omega}^*}$$

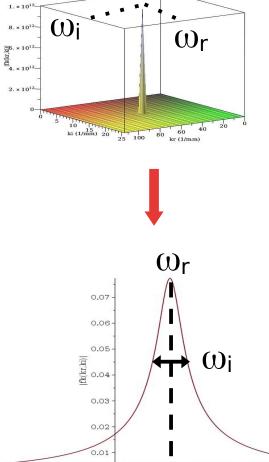


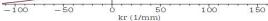


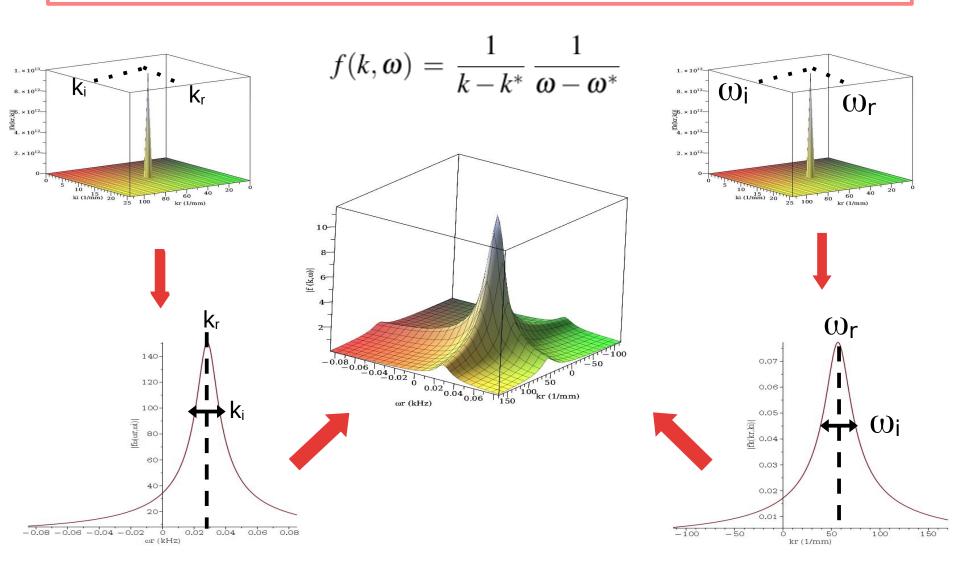


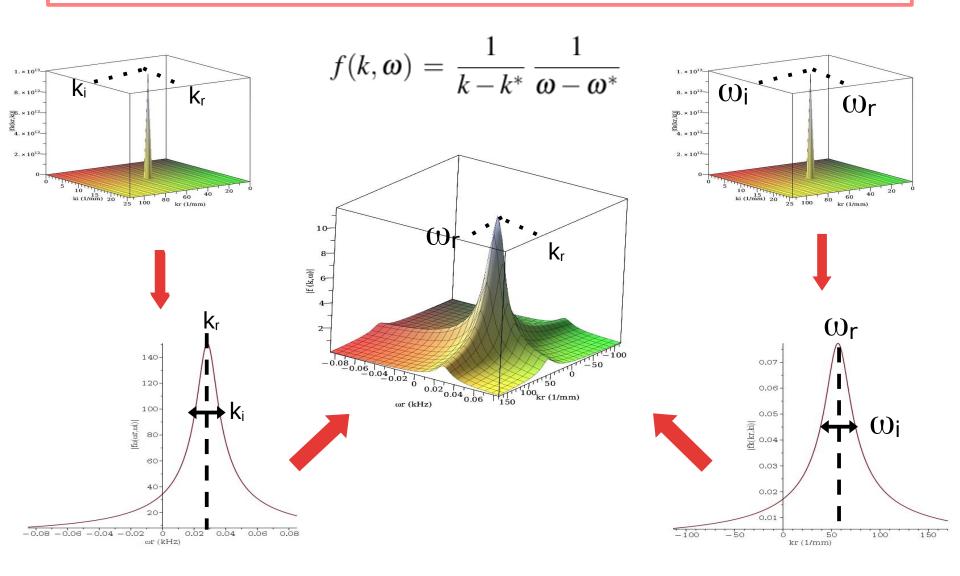


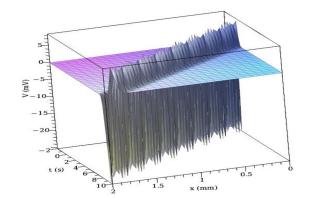
$$f(\boldsymbol{\omega}) = \frac{1}{\boldsymbol{\omega} - \boldsymbol{\omega}^*}$$

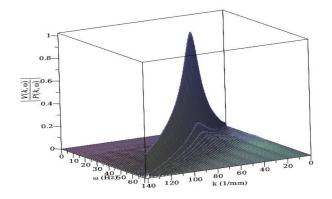


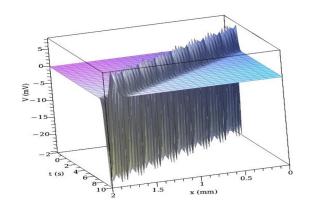


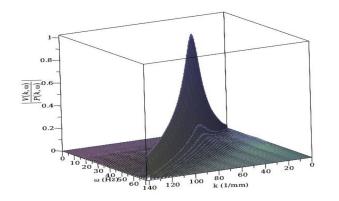




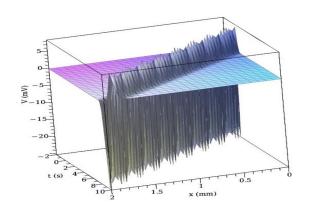


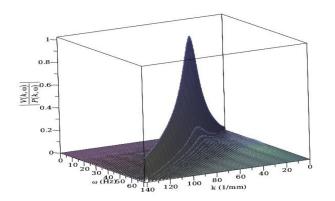




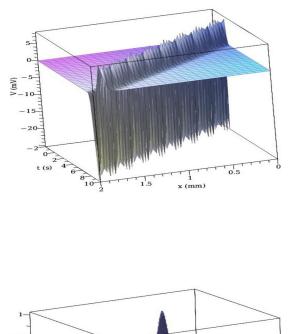


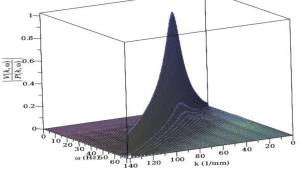
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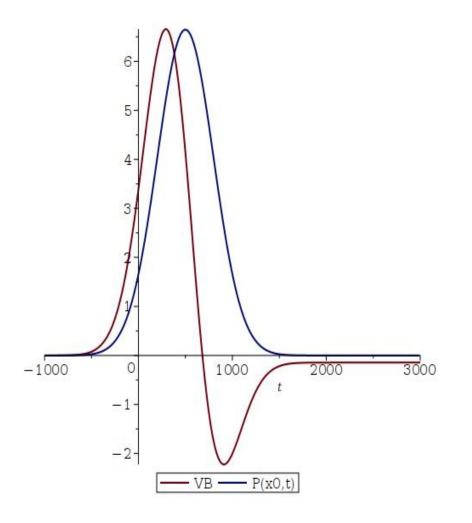
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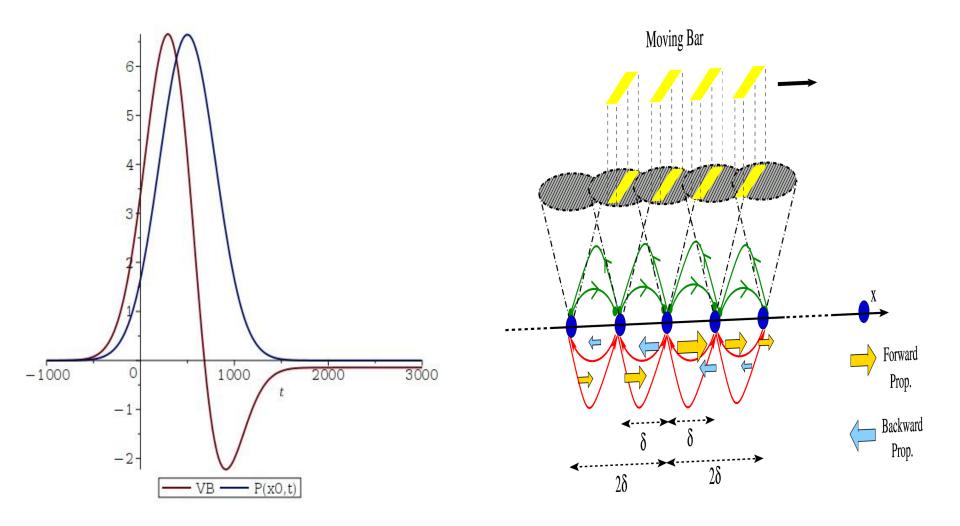
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Lateral inhibition can induce retinal anticipation



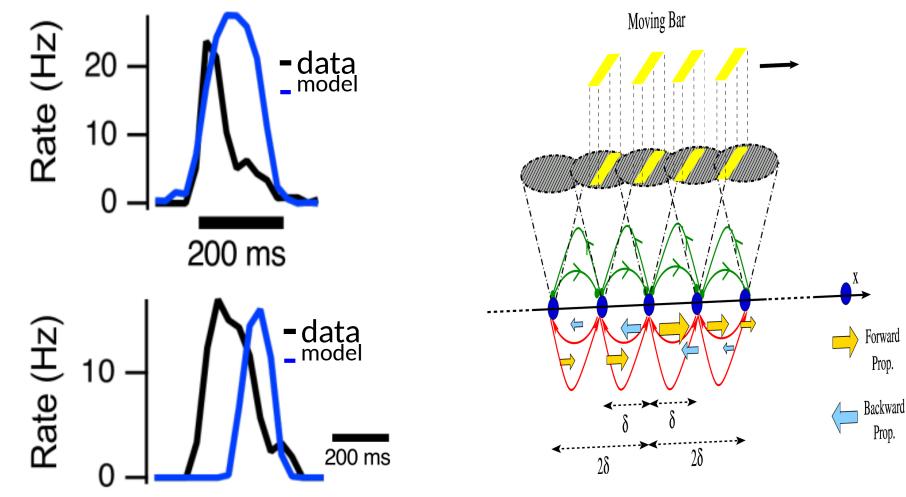
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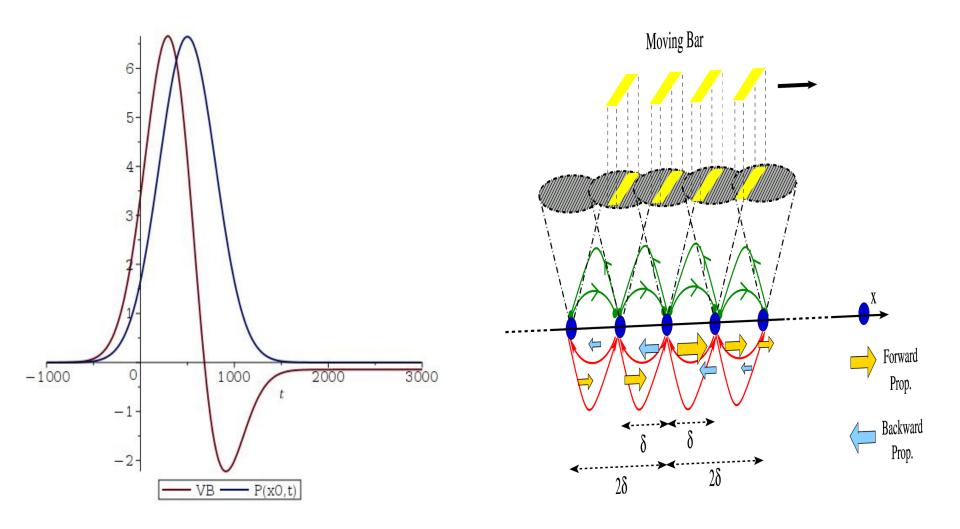
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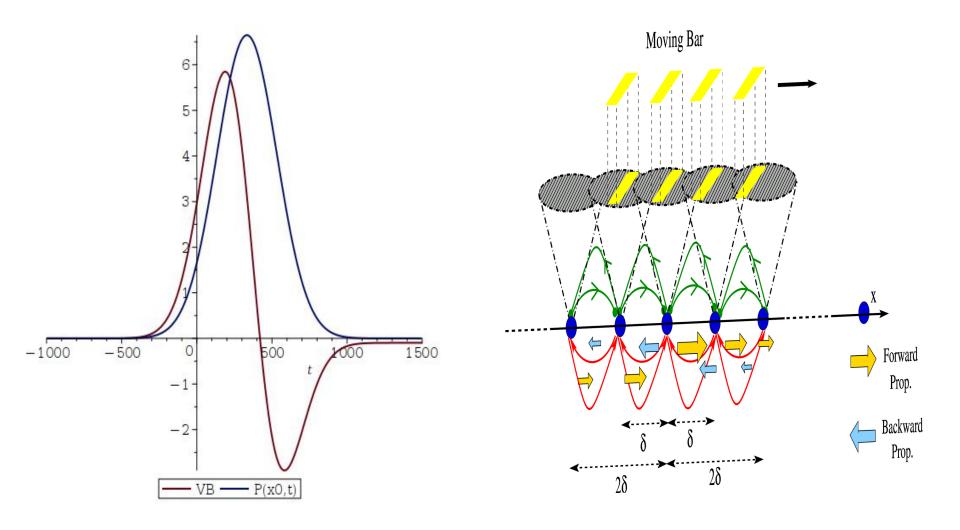


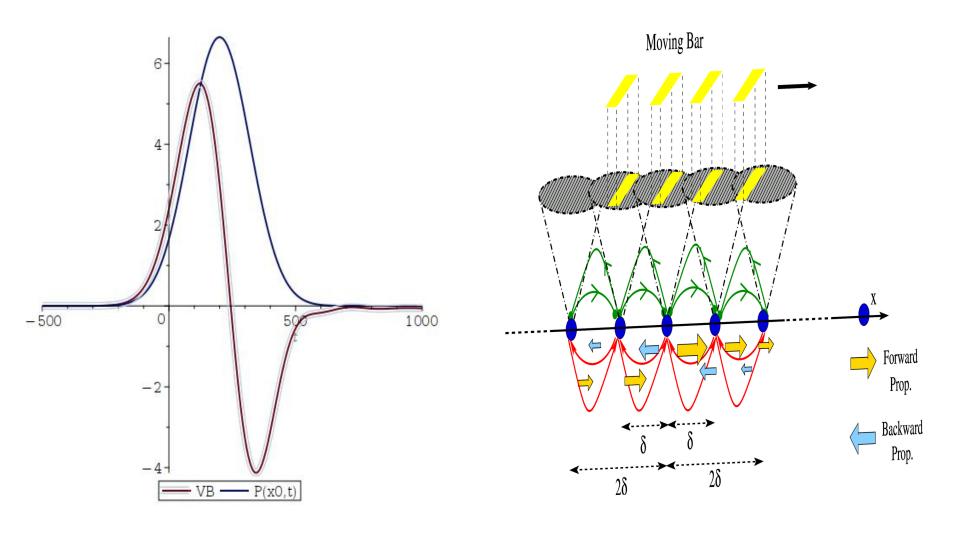
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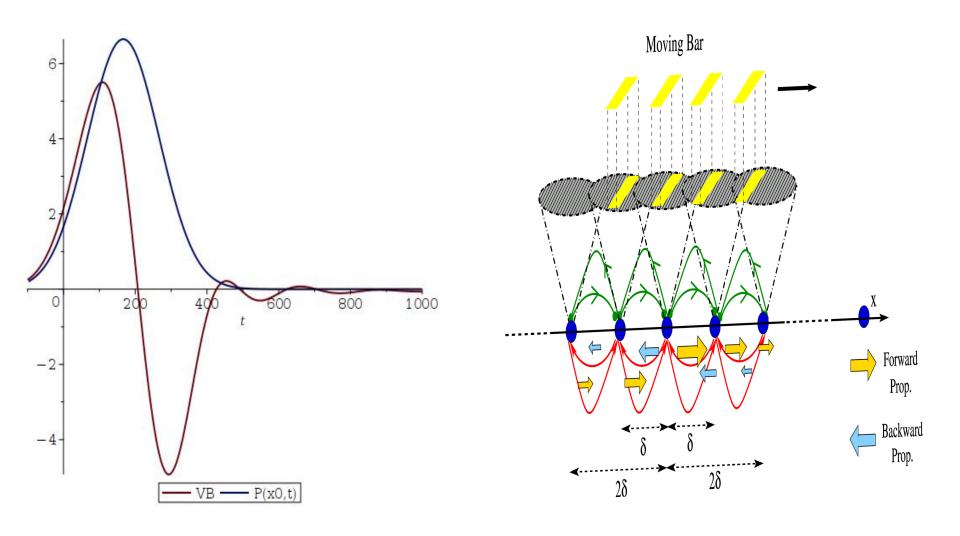
Adapted from M. Menz et al., bioRxiv (2020)

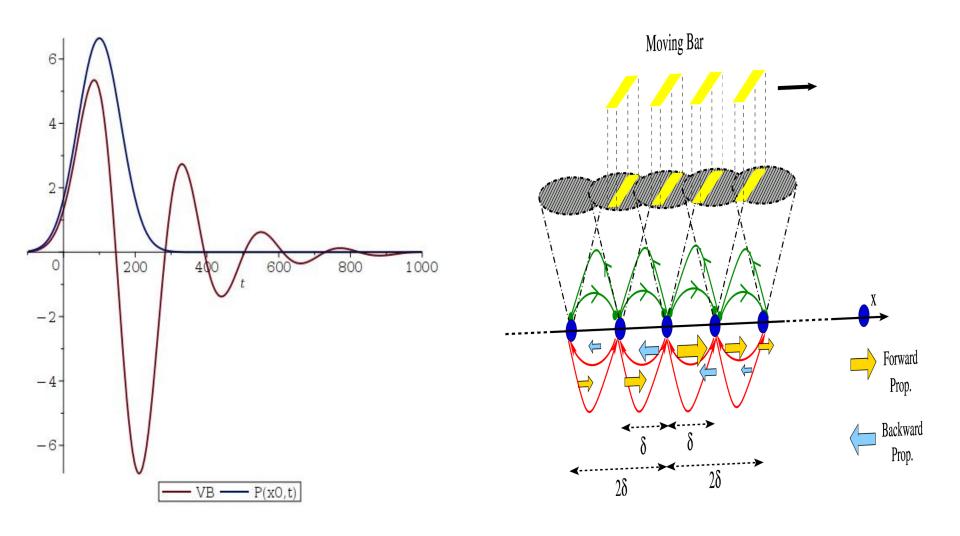


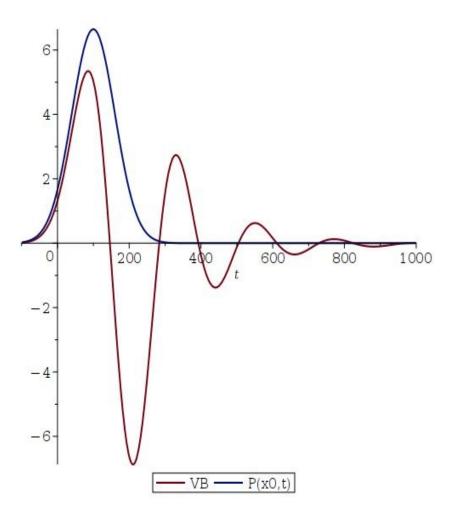












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How does lateral inhibition shape the response to moving stimuli ?



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 **spatio**-**temporal Fourier transform**.

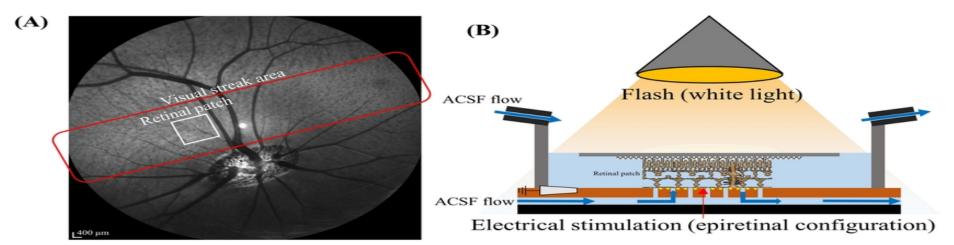
ESTHETICS/FUSION Projects

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**



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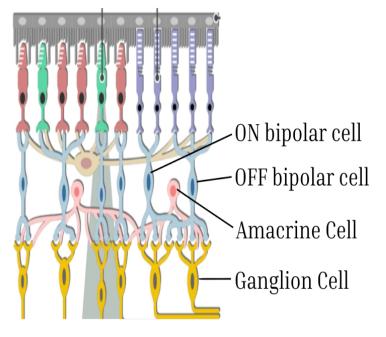
Recording start

Recording end

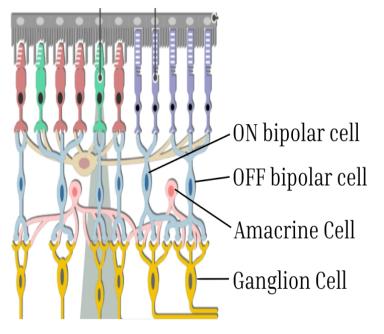
_ ↓	180 s	80 s	180 s		300 s	↓	
	Spontaneous firing	Light stimulation	Resting		Electrical		
		ON 2 s/OFF 2 s Total 20 trials Stimulus sequence		stimulation 15 different combinations of stimulus parameters Total 300 pulses Shape of a unit electrical pulse Amplitude (10 to 30 μA) Duration (0.5 to 2 ms)			
			Pulse duration (Stimulus sequence Pulse duration (ms)			
			0.5 m	ns	1 ms	2 ms	
10 μΑ[15 μΑ[20 μΑ[25 μΑ[30 μΑ]10 μΑ[15 μΑ[20 μΑ]25 μΑ[30 μΑ]10 μΑ]15 μΑ[20 μ						10 μA 15 μA 20 μA 25 μA 30 μA	

Pulse amplitude (µA)

Photoreceptors

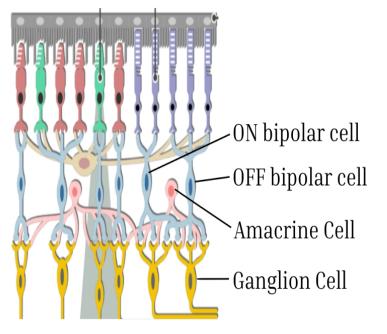


Photoreceptors



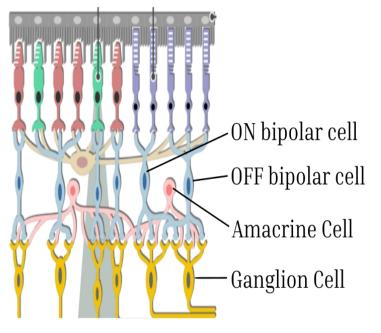
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Photoreceptors



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- 2 It is designed to respond optimally to complex **spatio-temporal** visual scenes **(motion)**.

Photoreceptors

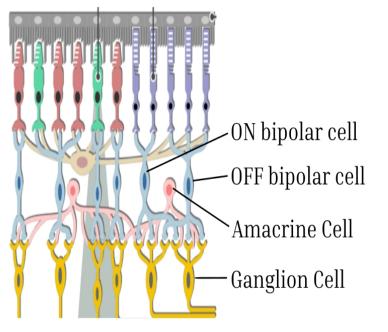


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3 The currently used stimuli have, either :

- a rather simple spatio-temporal structure (flashes, white noise, gratings, periodic illumination), or ;
- Too complex a structure (natural movies).
- Intermediate cases start to be analysed (moving bars).

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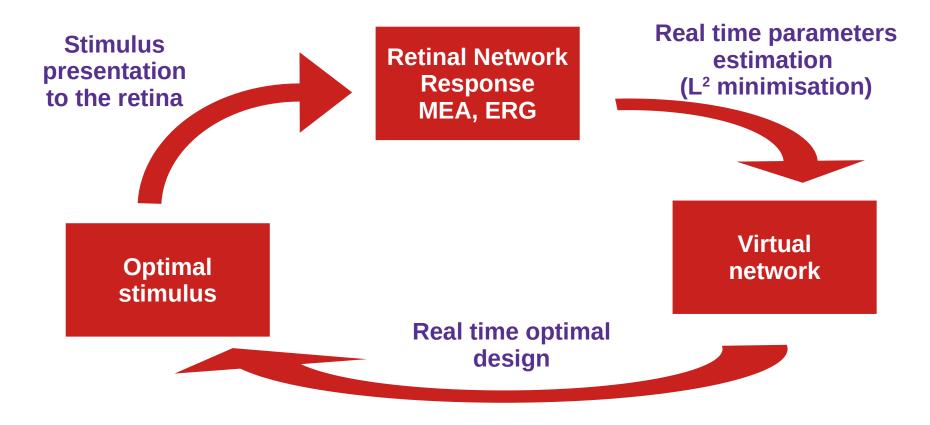
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Develop a new strategy, combining experiments and modeling, to better understand the retinal **network dynamics** using appropriate **spatio-temporal** stimuli and **closed loop** experiments.

Context

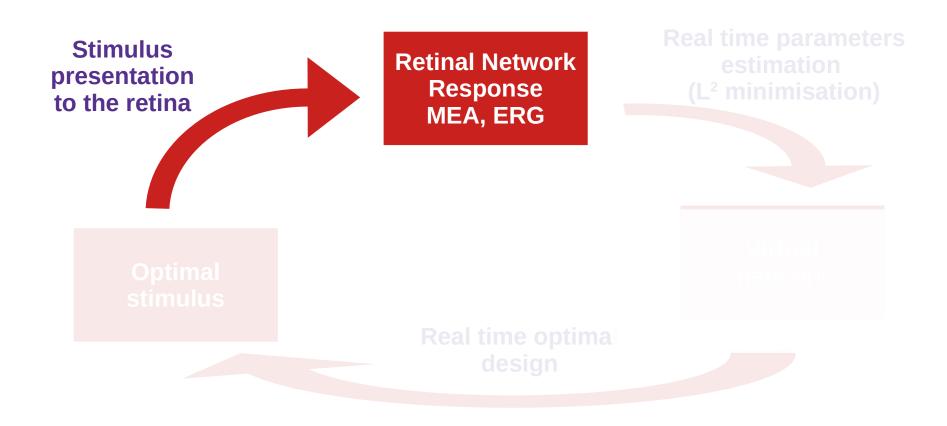
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Fundings : RISE, DocWalker, Associated INRIA Team Fusion, EDSTIC



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

- Design of simple stimuli;
- Experiments;
- First analyses.

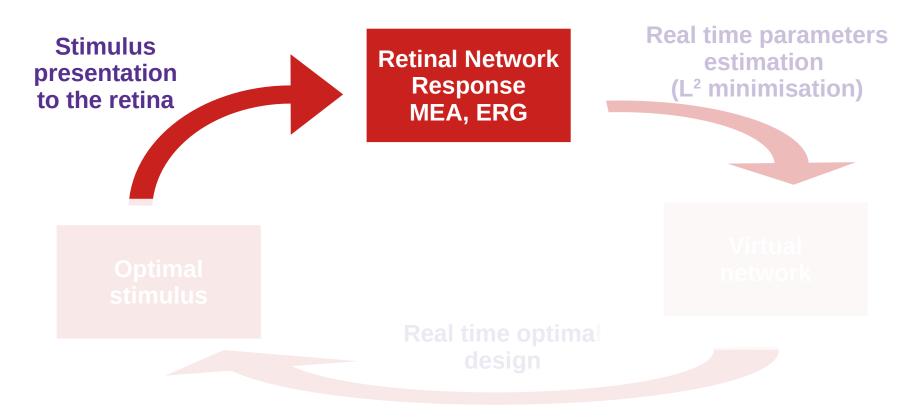


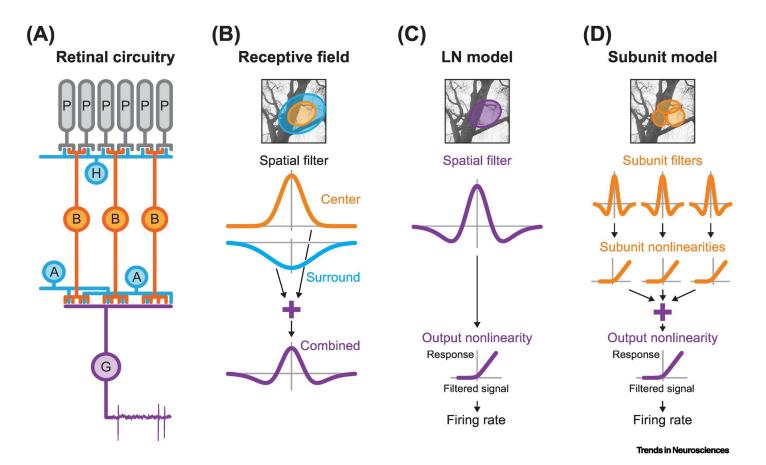
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2 Venue of F. Miqueles and J. Portal-Diaz at INRIA (Esthetics, Feb.-Apr. 2024):

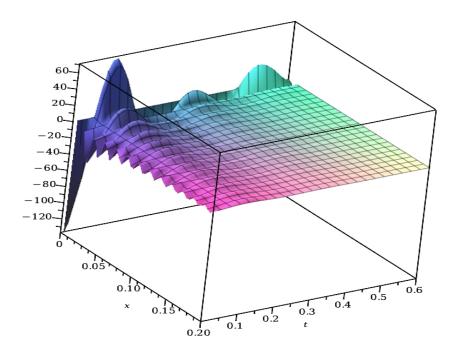
- Tools to analyse the spatio temporal information provided by raw data;
- Spatio temporal FFT, attempts to characterize a convolution kernel;
- Spikes in ERG;
- Parameters estimation + stimulus design.





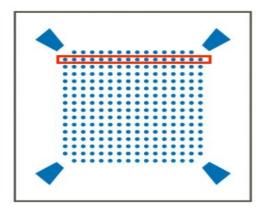
Zapp, Sören J. et al. Trends in Neurosciences, Volume 45, Issue 6, 430 - 445

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

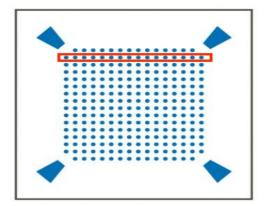


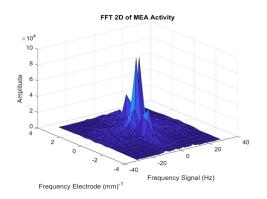
- S. Souihel, B. Cessac, Journal of Mathematical Neuroscience, 2021, 11
- B. Cessac, Journal of Imaging, 2022, 8 (1)
- E. Kartsaki, G. Hilgen, E. Sernagor, B. Cessac, Neural Computation, 2024, 36 (6)
- S. Ebert, T. Buffet, B. S. Sermet, O. Marre, B. Cessac, Nature Com., 2024, 15 (6118)

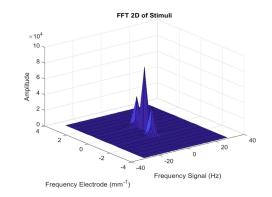
The behaviour of the **retinal network** is characterized by a cascade of convolutions and weak non linearities.



A Multi-Electrode Array naturally provides a spacetime sampling of the retinal response.

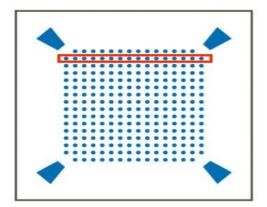


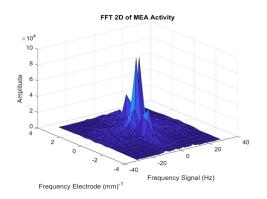


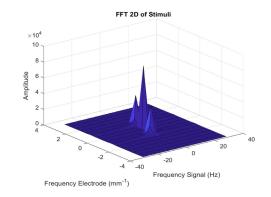


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$$V_{MEA}(t) = \left[K_{MEA} \overset{x,y,t}{*} \mathcal{S}\right](t)$$

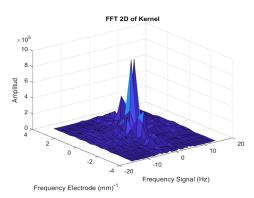


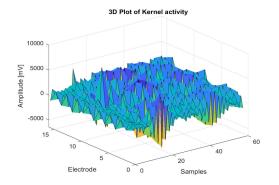


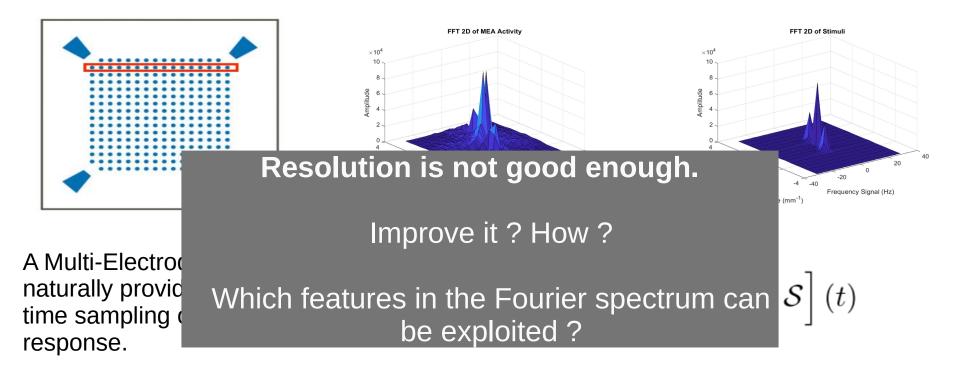


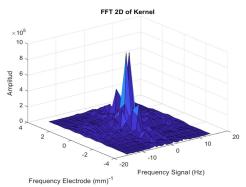
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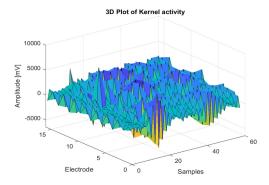
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- Explicit computation of a spatio-temporal kernel featuring the retina response
- Property of the Fourier Transform
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- Simulations on the Macular simulator.

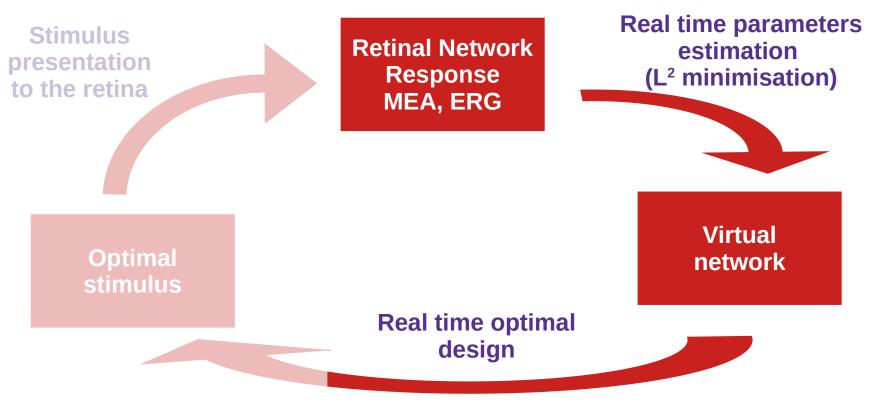
Retinal Network Response MEA, ERG

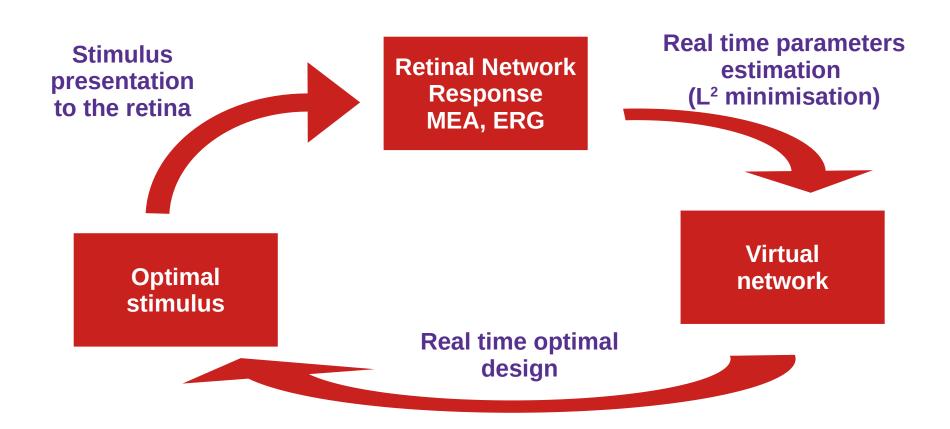




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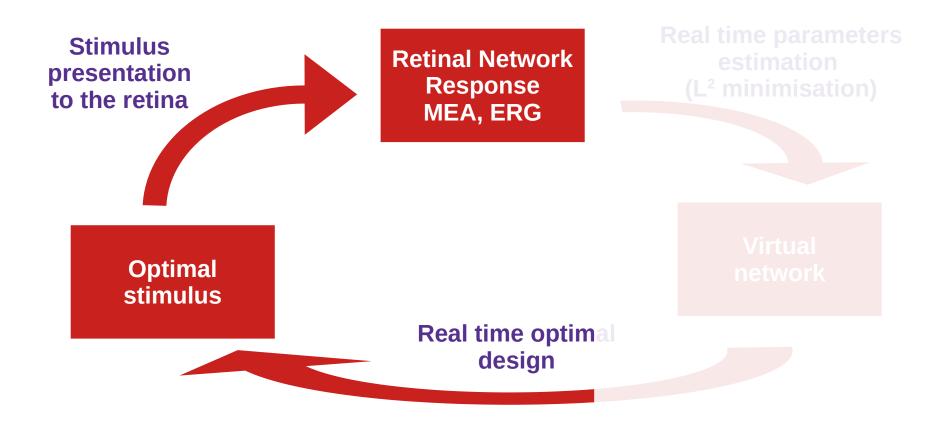
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 - ANR project lead by L. Sacchelli





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- Attend experiments, learn how to handle data, how to efficiently interact given the distance.
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- Stimuli design.

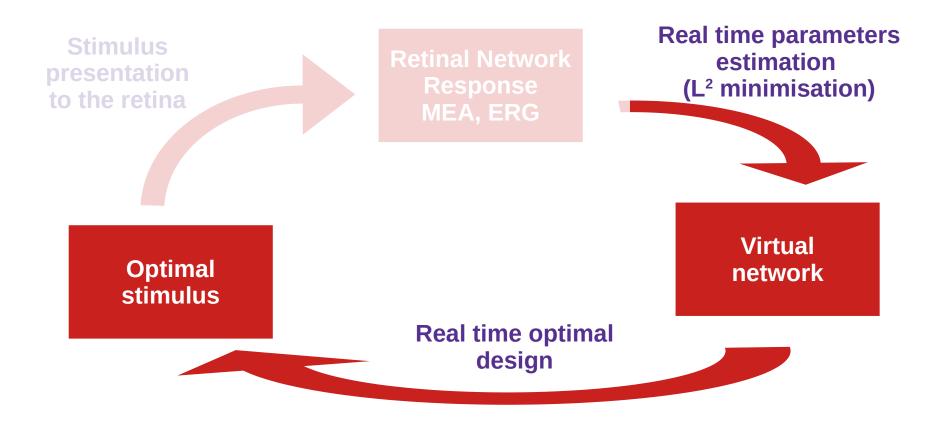


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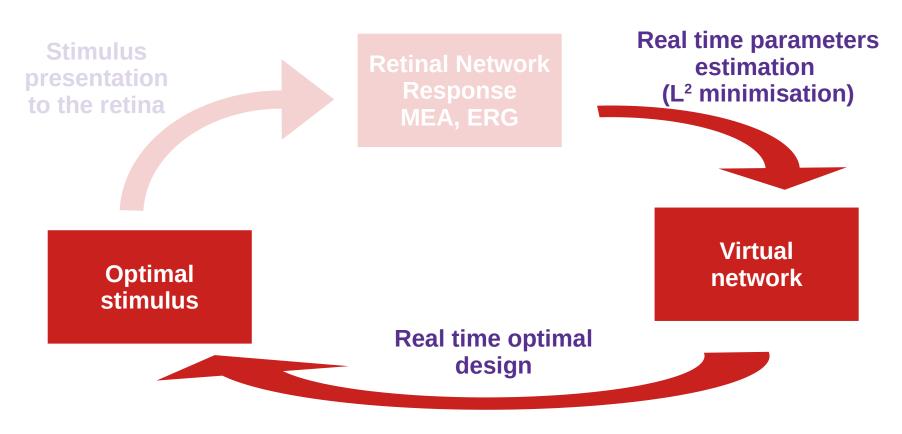
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Bibliography

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.

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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 ?

Thanks