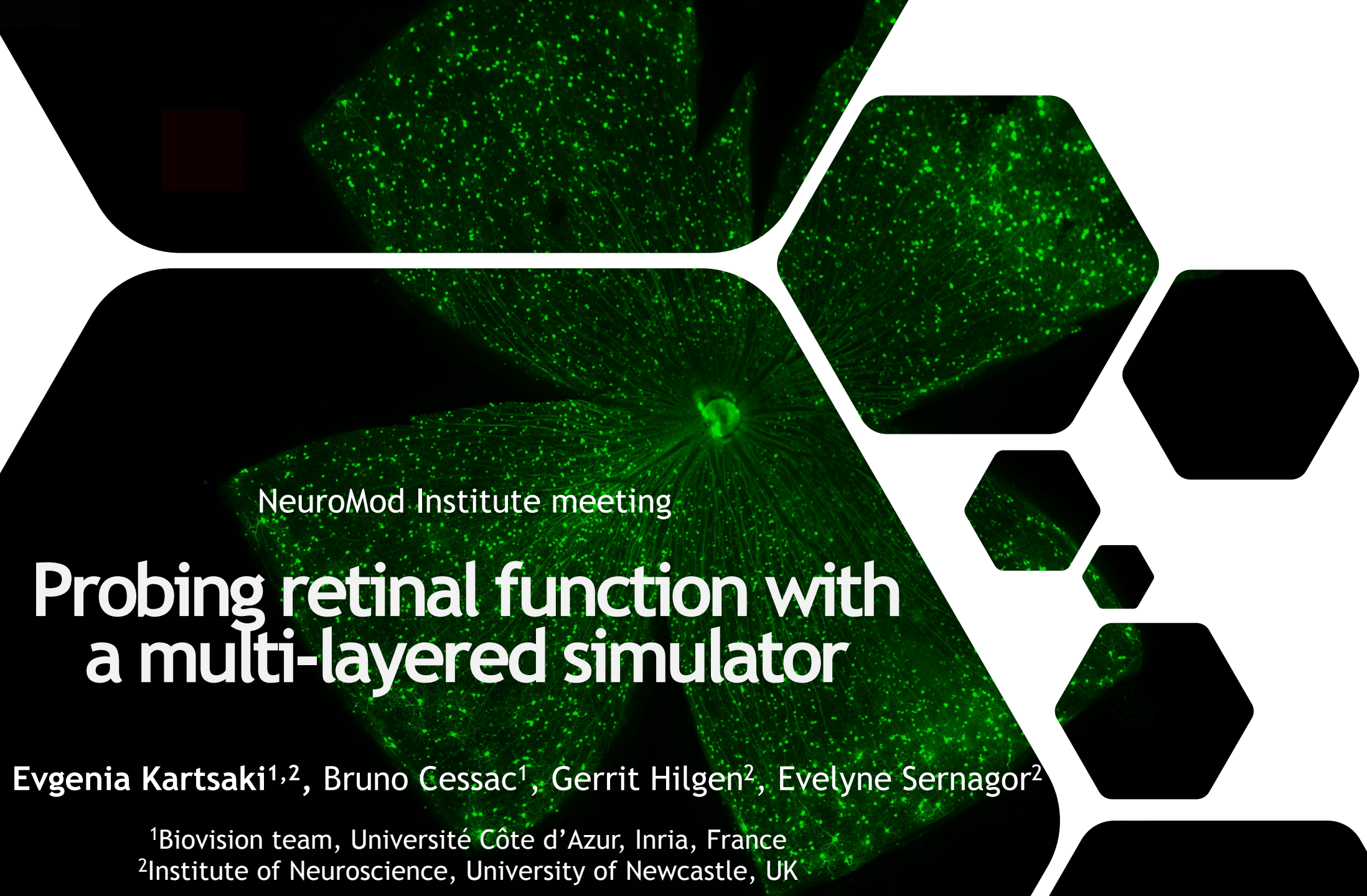
Probing retinal function with a multi-layered simulator

Evgenia Kartsaki, Bruno Cessac, Gerrit Hilgen, Evelyne Sernagor

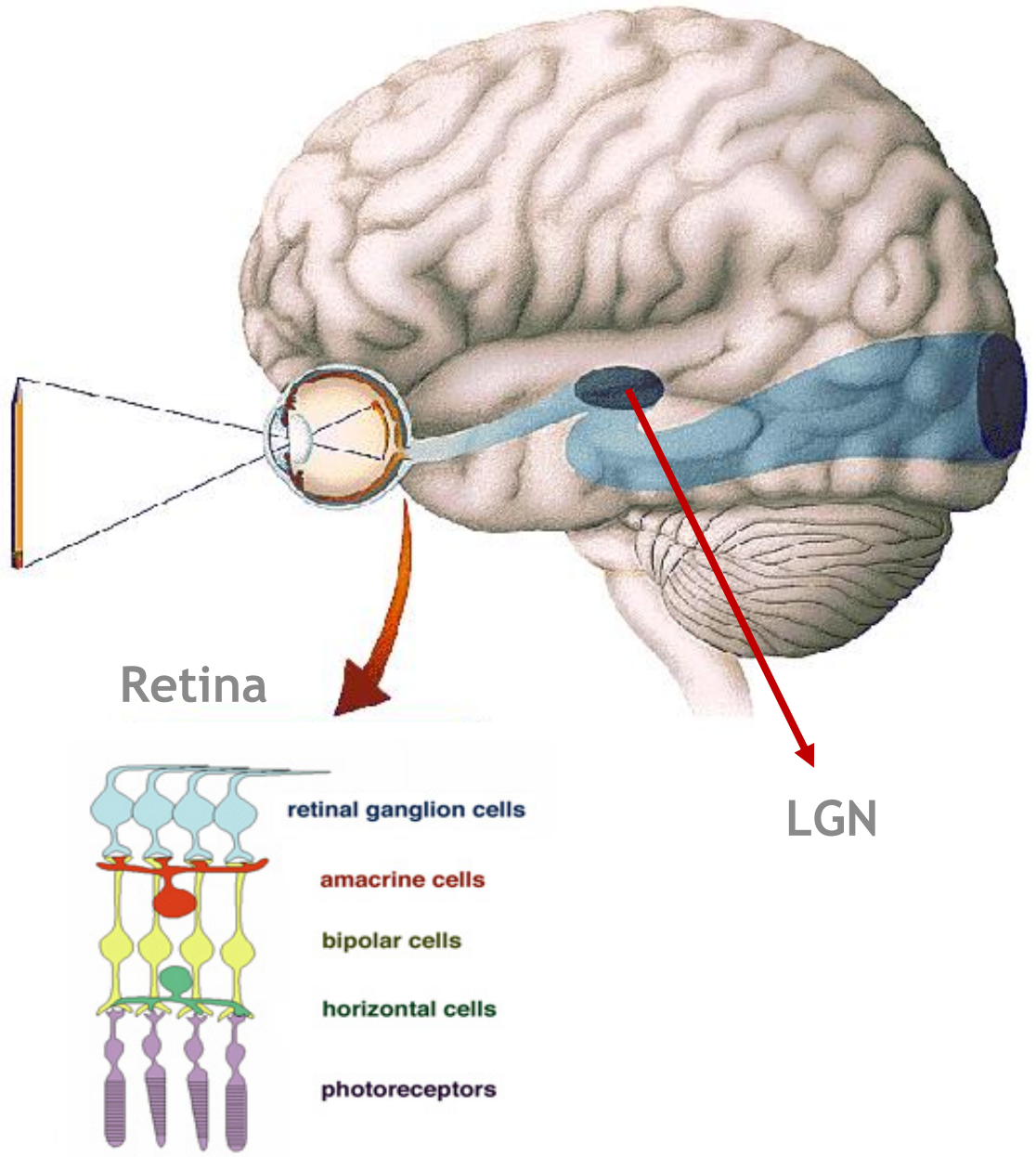


NeuroMod Institute meeting

Probing retinal function with a multi-layered simulator

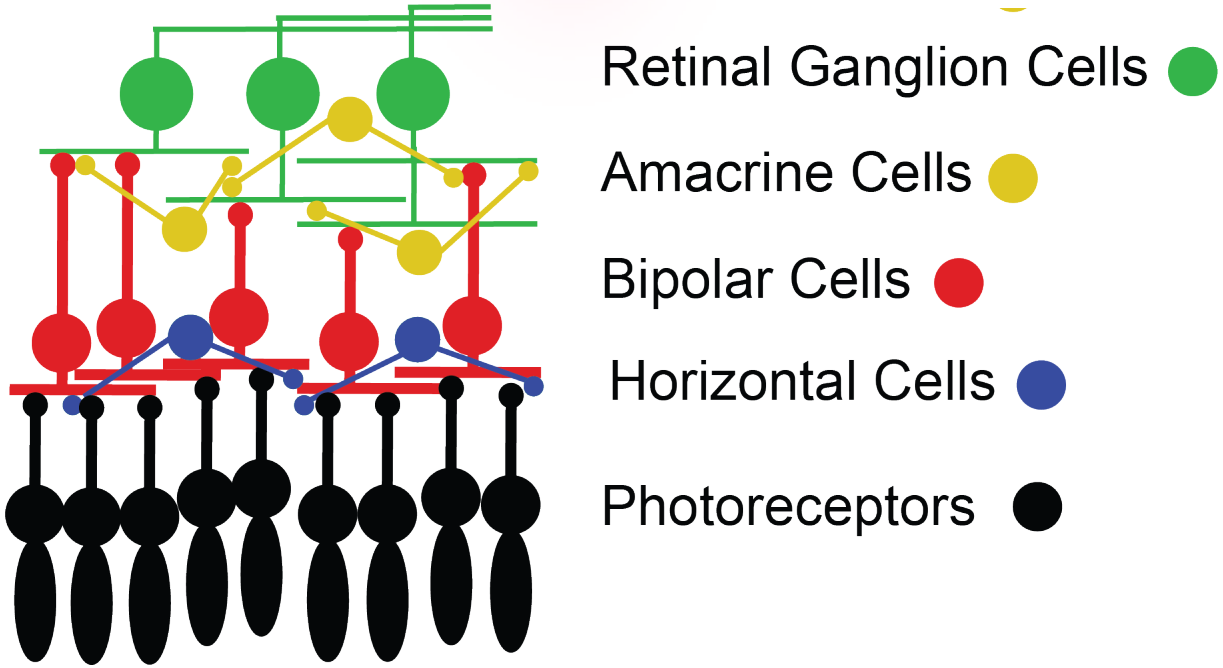
Evgenia Kartsaki[1,2], Bruno Cessac[1], Gerrit Hilgen[2], Evelyne Sernagor[2]

[1]Biovision team, Université Côte d'Azur, Inria, France
[2]Institute of Neuroscience, University of Newcastle, UK



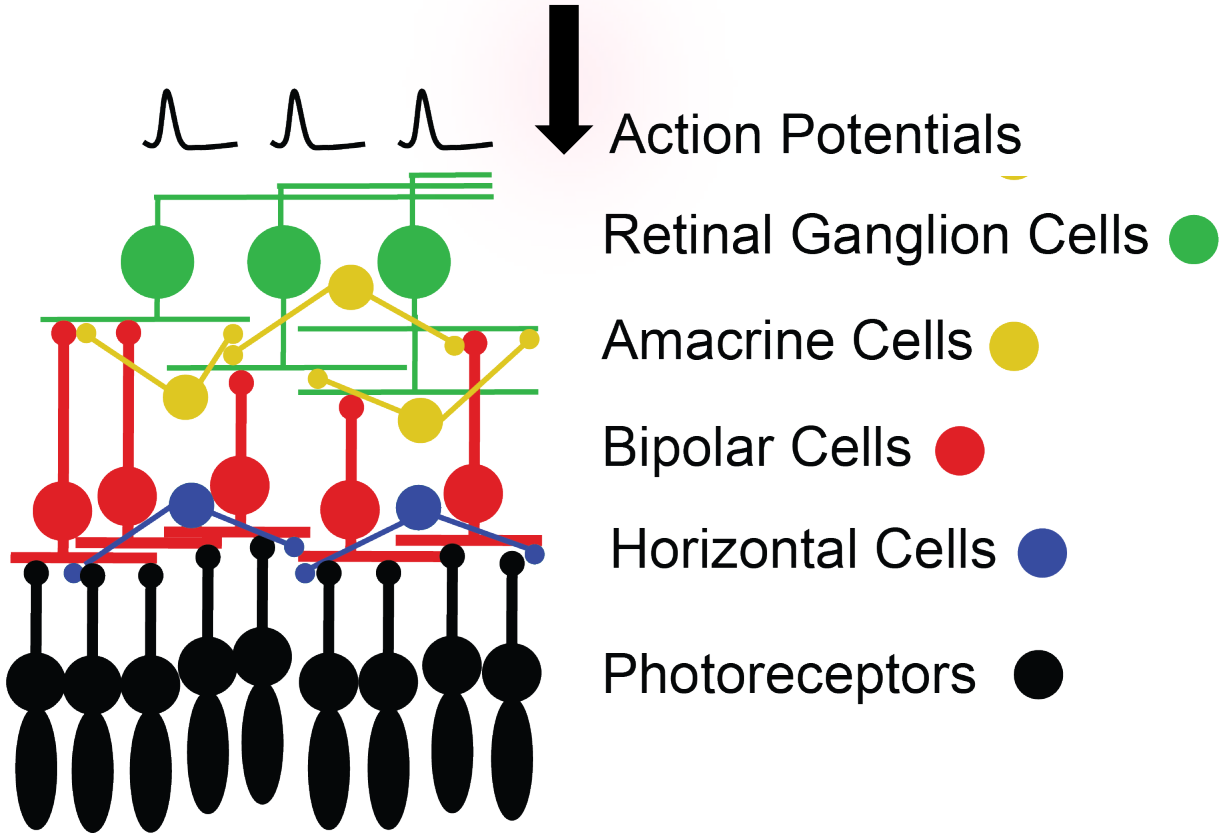
source: Howard Hughes Medical Institute

Retinal visual flow



Source: ETH Zürich

Retinal visual flow



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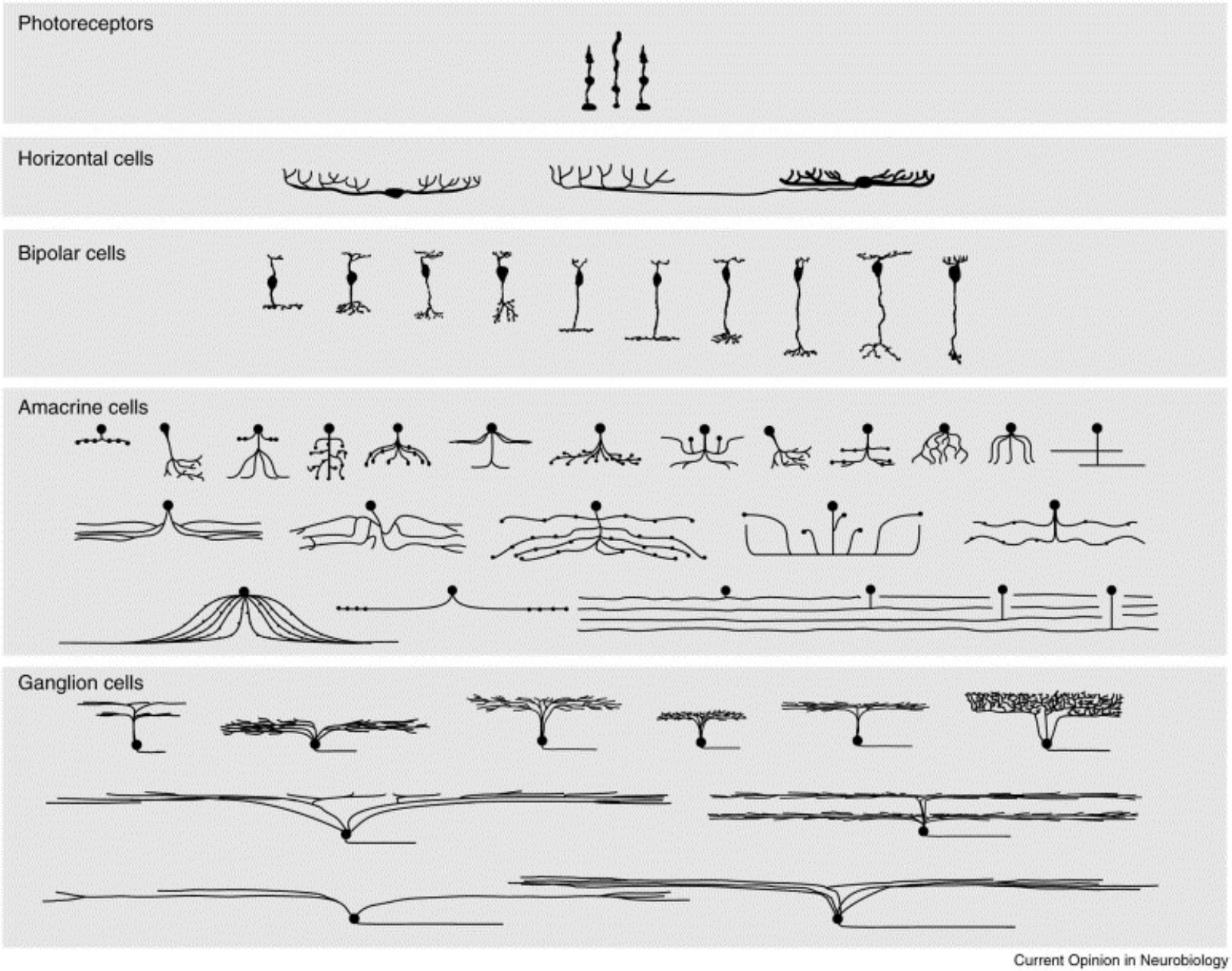


Retinal neurons inventory

Source: Masland et al., 2001

Leverhulme funded project:
"A novel approach to functional classification of retinal ganglion cells"

☞ Achieve full characterisation of retinal ganglion cells sub-classes based on:

- pharmacogenetics
- large-scale retinal electrophysiology
- immunochemistry

☞ Understand their role in population encoding of complex visual scenes

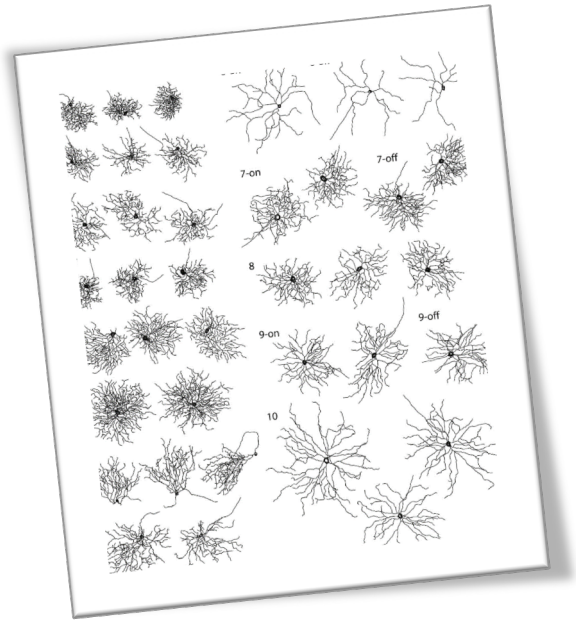
LEVERHULME TRUST

Newcastle University Institute of Neuroscience

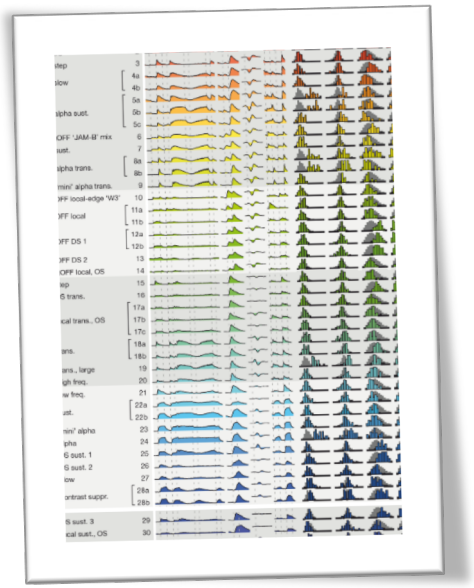
informatiques mathématiques Inria

UNIVERSITÉ CÔTE D'AZUR

Yet another RGC classification…



Coombs et al., 2006



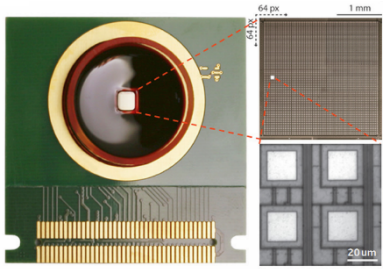
Baden, Berens, Franke et al., 2016

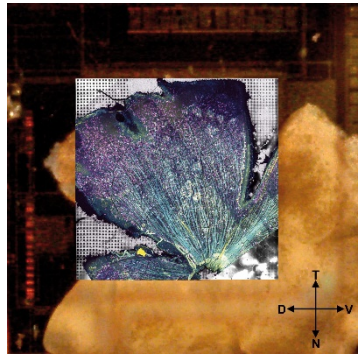
Martersteck, Hirokawa, Evarts et al., 2017

- Novel and interdisciplinary
- Combines shared gene expression with physiology and parts of anatomy

Aims

- Identify RGCs sharing a common gene expression by combining *pharmacogenetics*, large-scale high-density *electrophysiology* and *immunohistochemistry*





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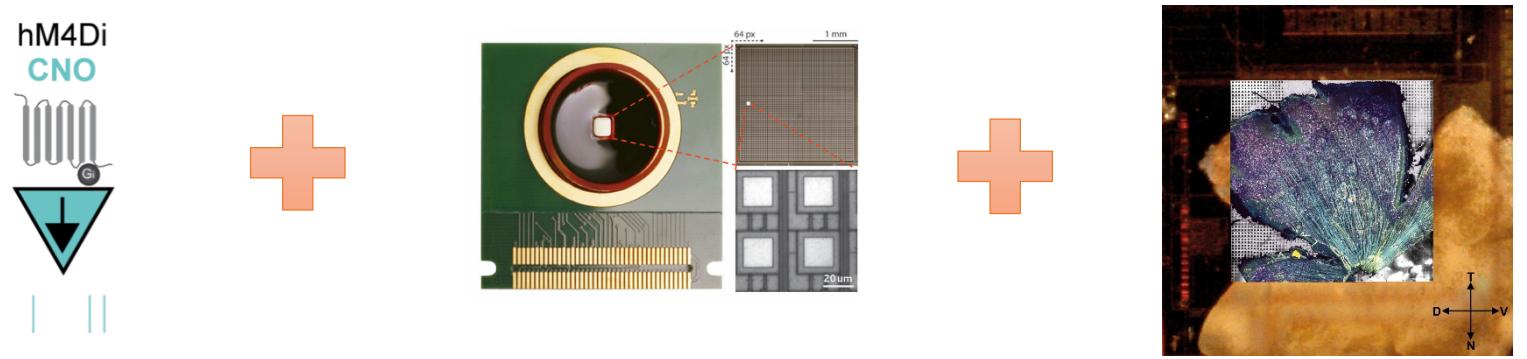

- Isolate subgroups from that RGC pool based on responses to different stimuli

Aims

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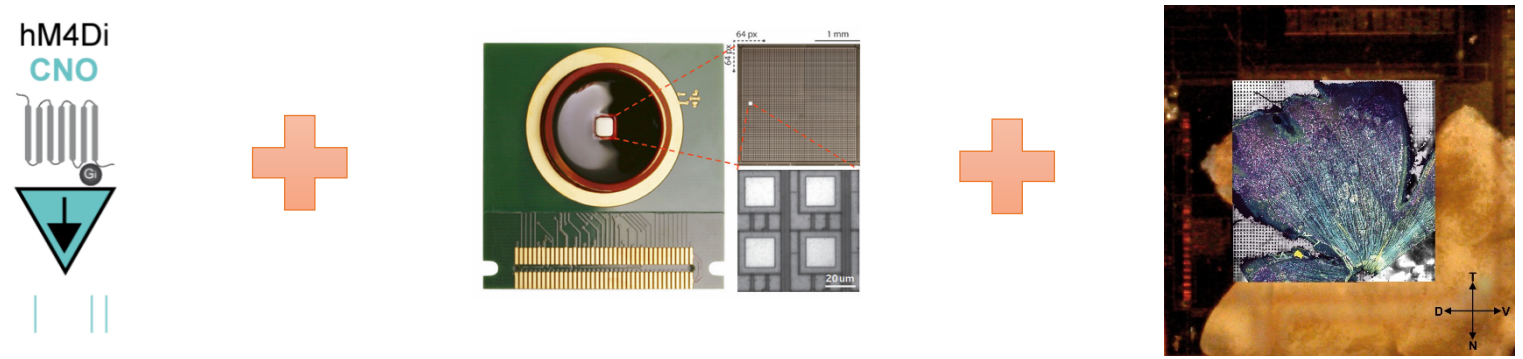

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- Unravel how RGCs in these subgroups respond and interact to basic and complex visual scenes

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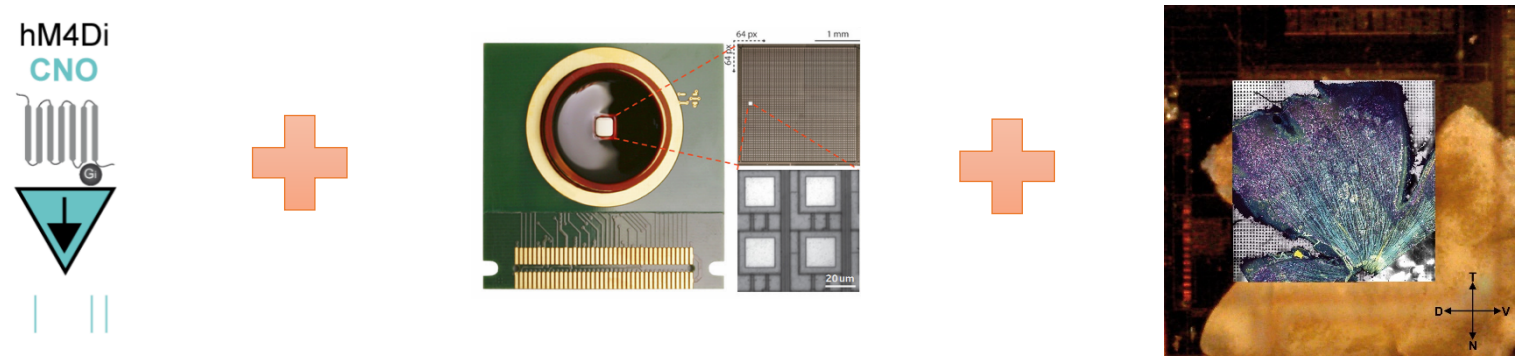


- Isolate subgroups from that RGC pool based on responses to different stimuli

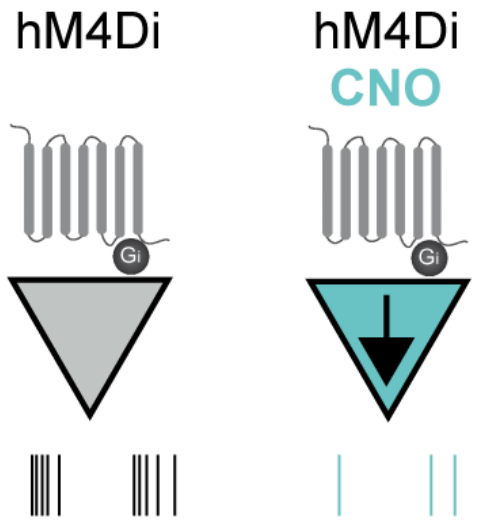
- Unravel how RGCs in these subgroups respond and interact to basic and complex visual scenes

→ Modelling

→ Numerical simulations

Pharmacogenetics - DREADD technology

Designer **R**eceptors **E**xclusively **A**ctivated by **D**esigner **D**rugs

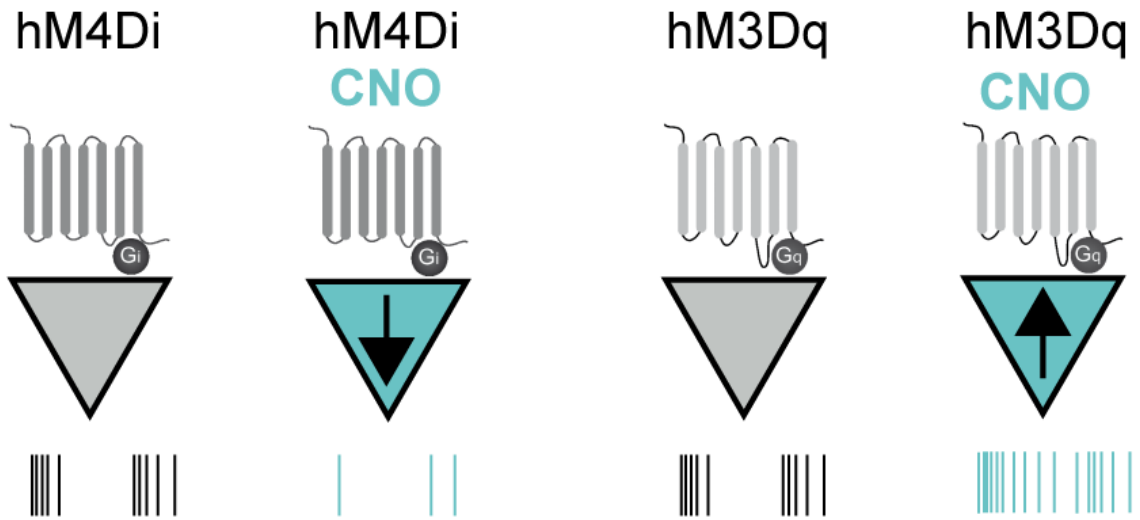


inhibitory DREADD ↘

Courtesy of Gerrit Hilgen

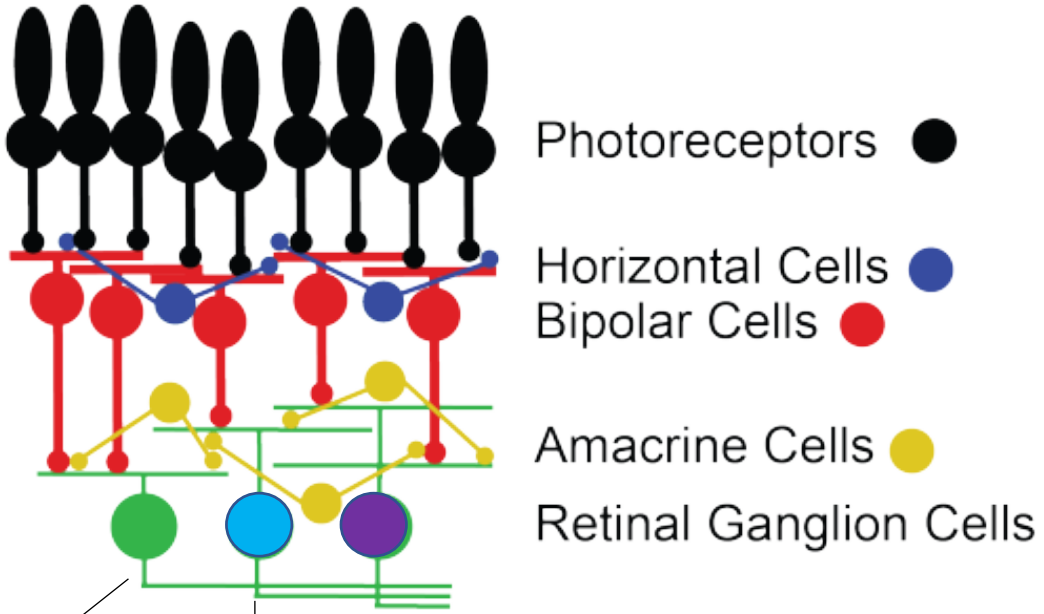
Pharmacogenetics - DREADD technology

Designer **R**eceptors **E**xclusively **A**ctivated by **D**esigner **D**rugs

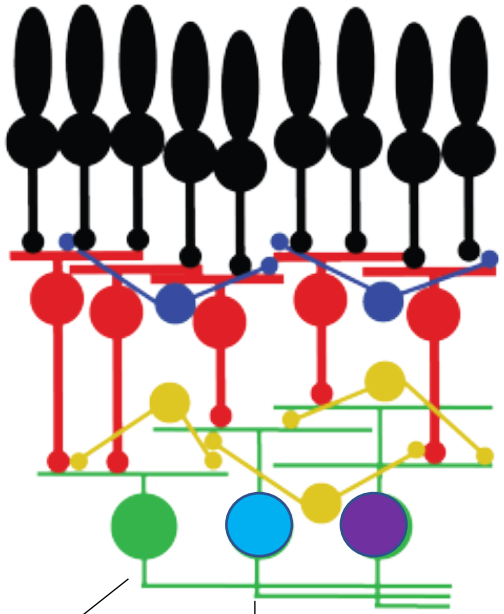


inhibitory DREADD ↘ excitatory DREADD ↗

Courtesy of Gerrit Hilgen

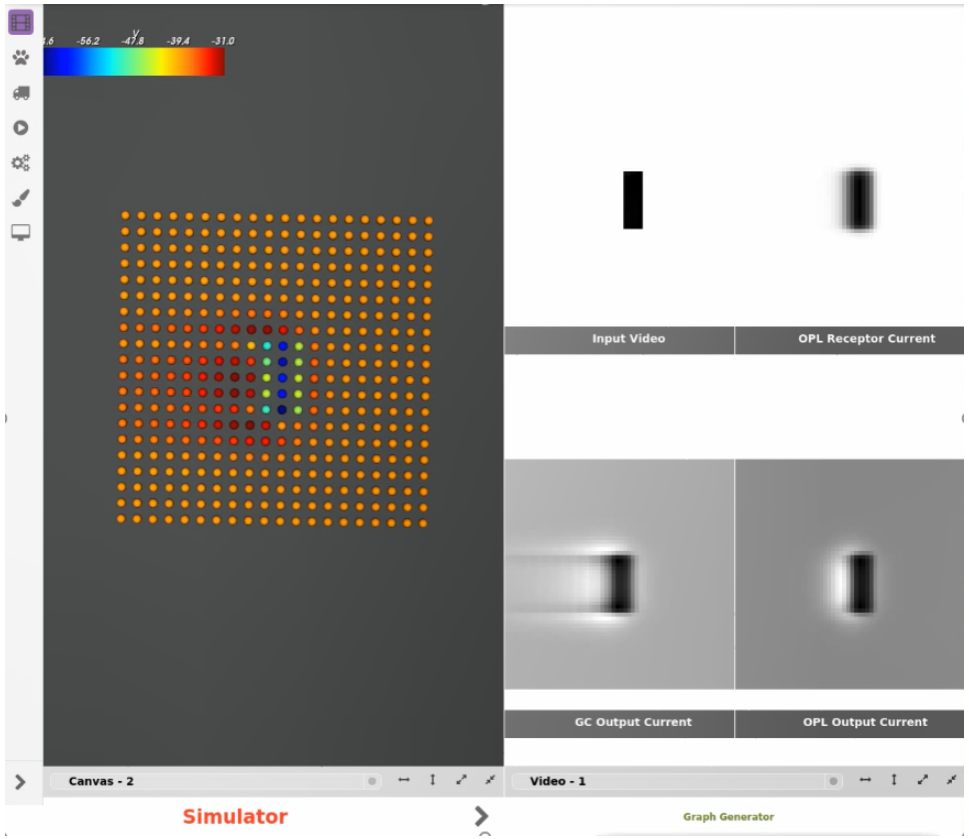


Source: ETH Zürich & RavaAzeredo da Silveira et al., 2011



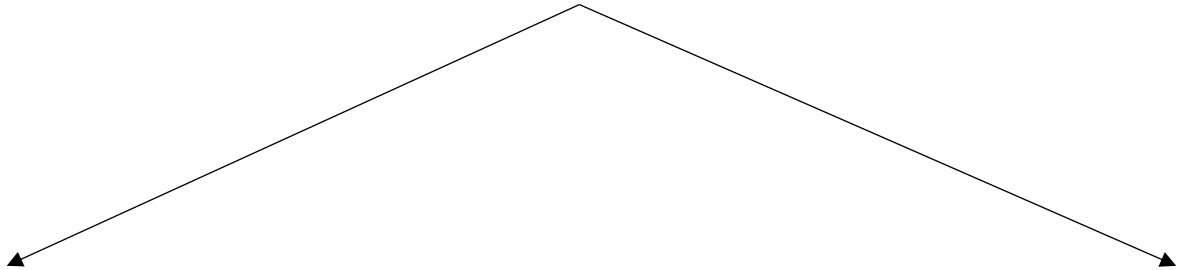
$$\frac{dy}{dx}$$

Macular



Source: ETH Zürich & RavaAzeredo da Silveira et al., 2011

Image motion



Global motion

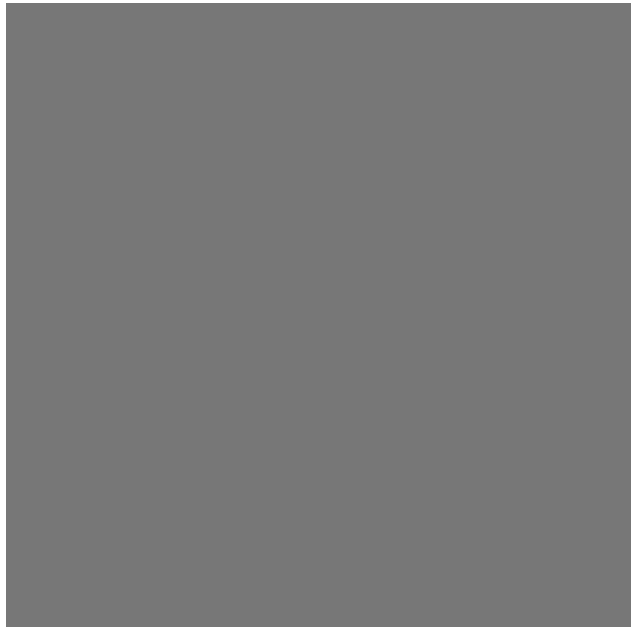
movement of body, head, or eye of the observer

Differential motion

motion of objects within the scene

Global motion

Differential motion



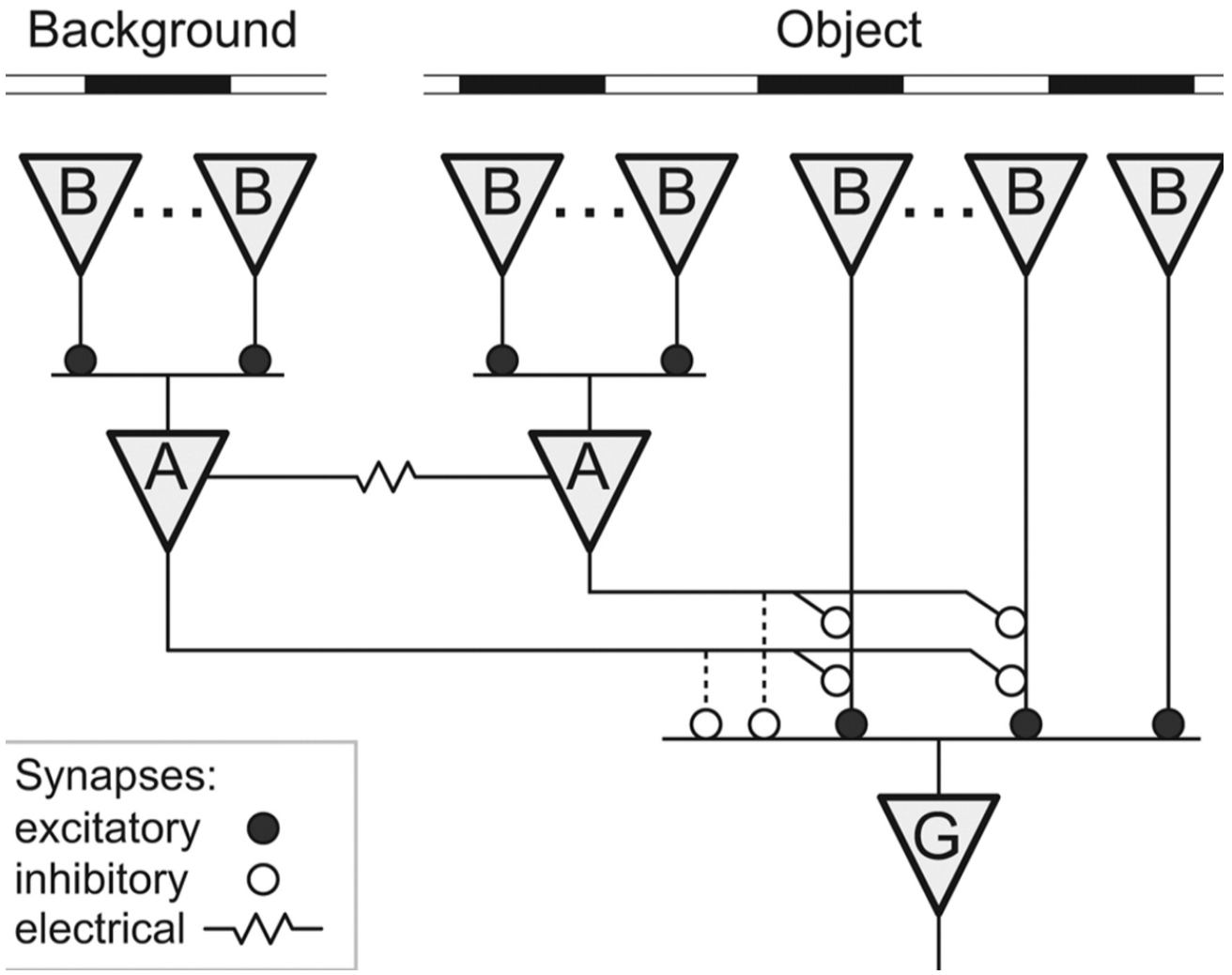
Static background – Object moving

Background & Object moving

Retinal circuit related to motion

Object region: Excitatory input to the ganglion cell (G) from many fast bipolar cells (B).

Background region: Inhibitory input to the ganglion cell (G) from amacrine cells (A).

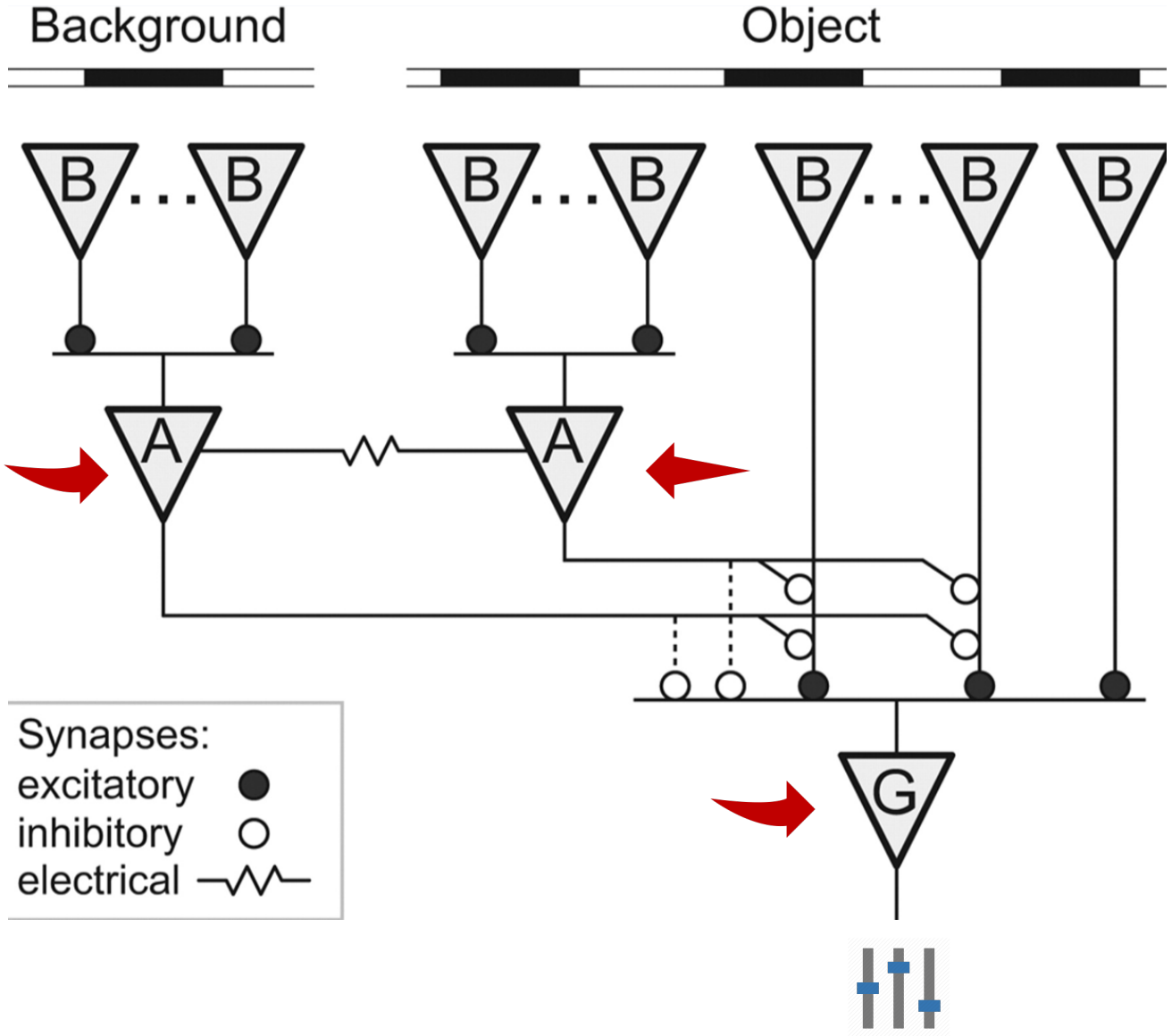


Inspired from Baccus et al., 2008

CNO effect on the circuit

DREADDs on :

- Amacrine cells (ACs) and/or
- Ganglion cells (RGCs)

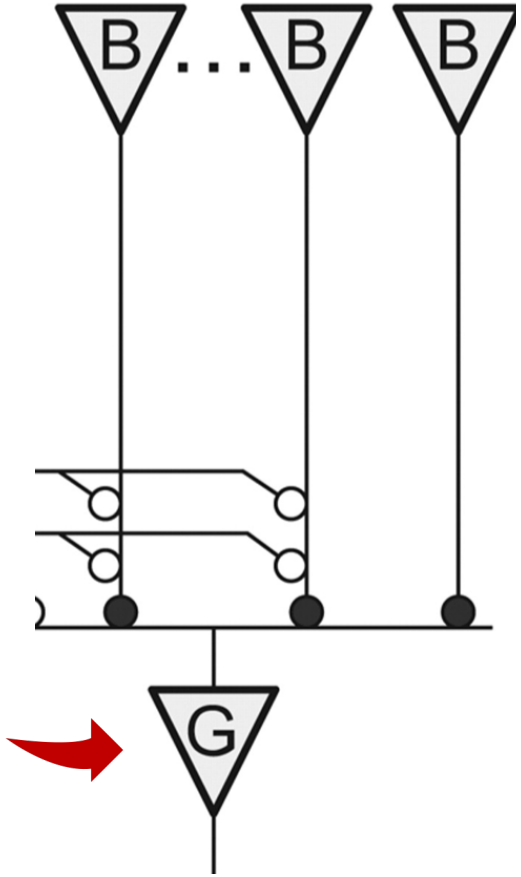


Inspired from Baccus et al., 2008

CNO effect on the circuit

DREADDs on Ganglion cells (RGCs)

- If excitatory, the neuronal activity will increase
- If inhibitory, the neuronal activity will decrease

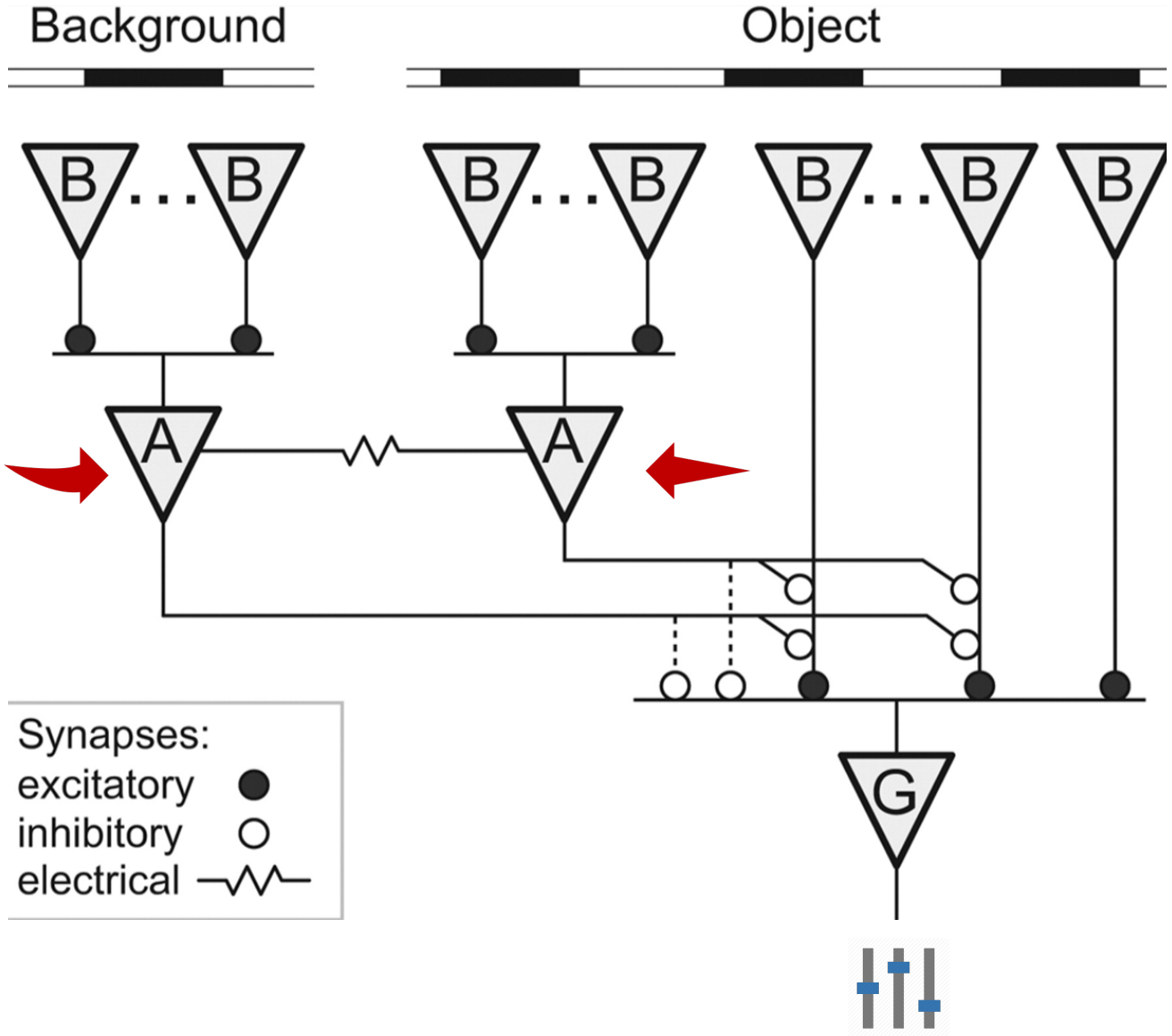


Inspired from Baccus et al., 2008

CNO effect on the circuit

DREADDs on Amacrine cells (ACs):

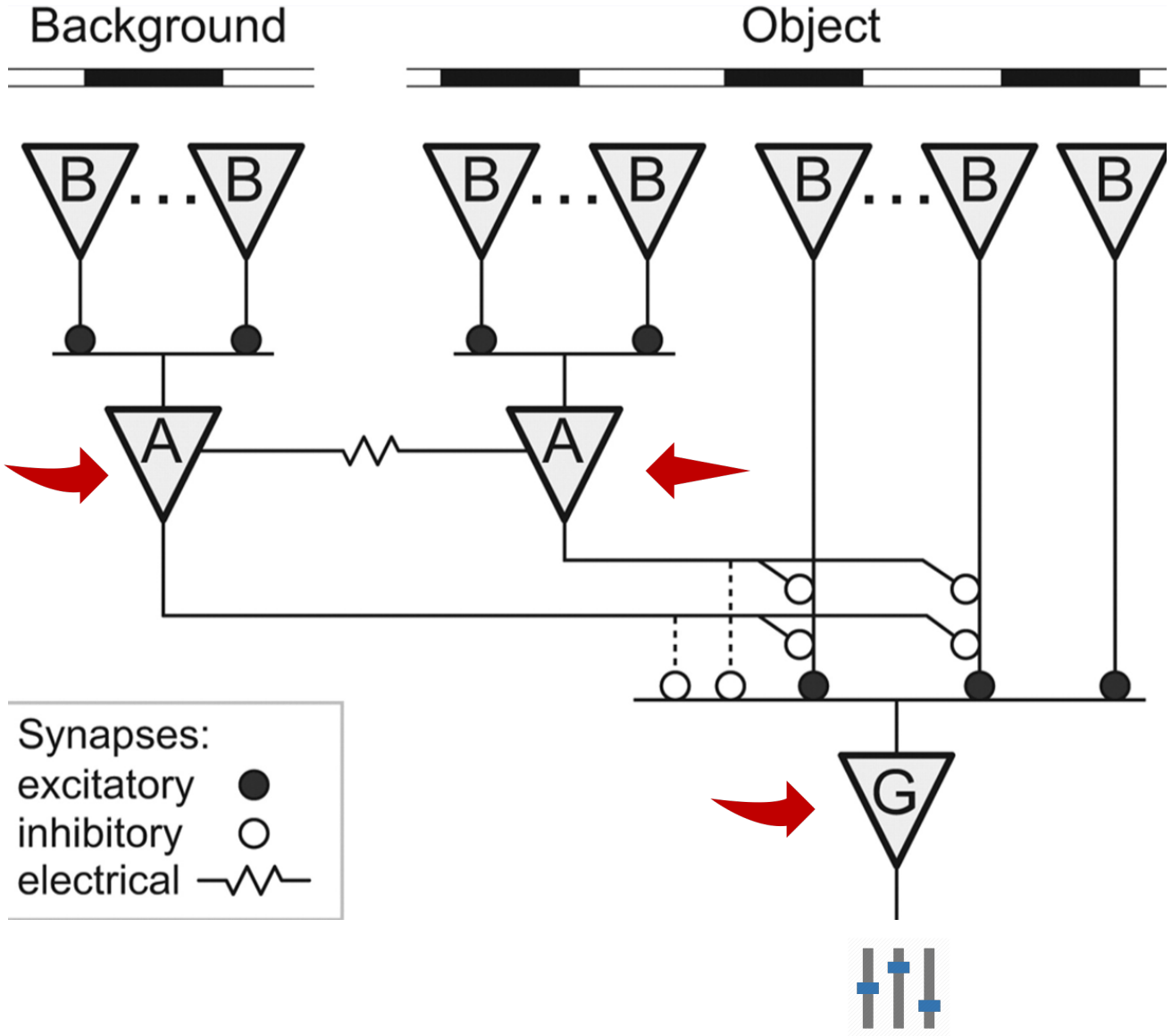
- If excitatory, the neuronal activity of G will decrease
- If inhibitory, the neuronal activity of G will increase



Inspired from Baccus et al., 2008

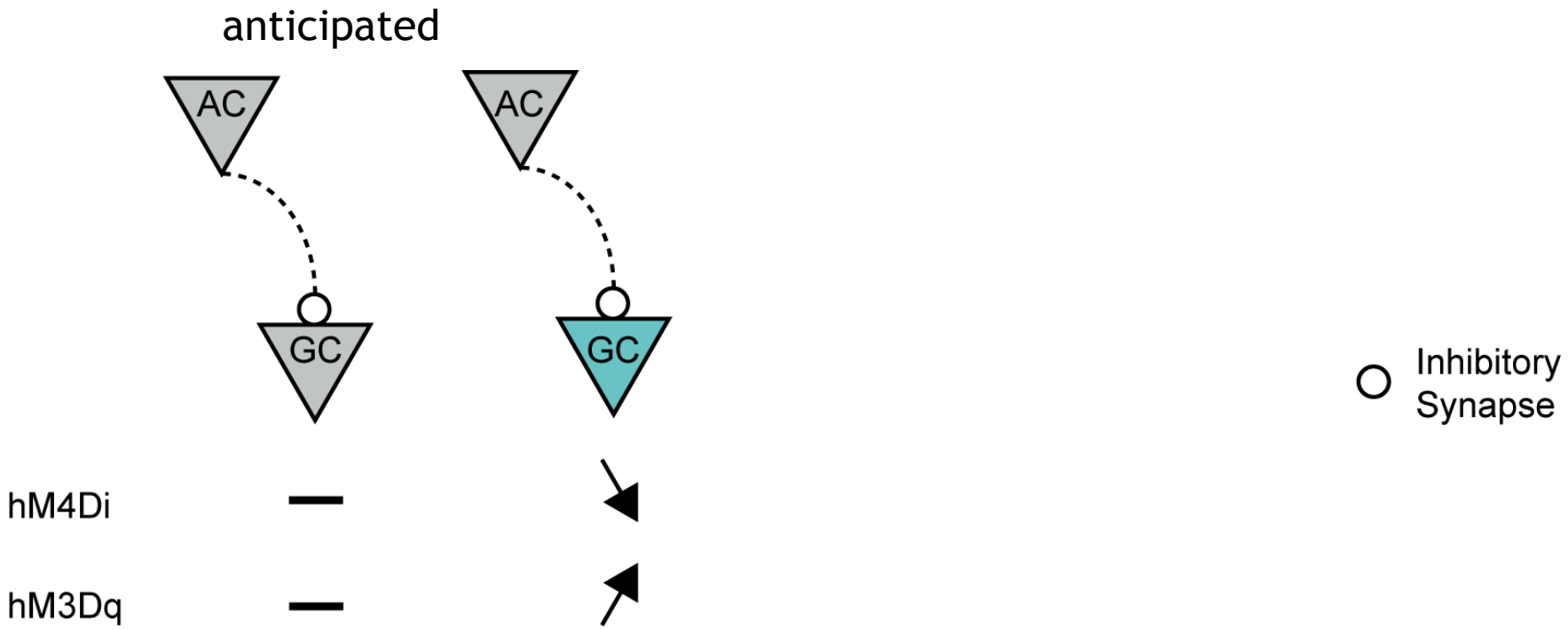
CNO effect on the circuit

DREADDs on : ACs AND RGCs



Inspired from Baccus et al., 2008

Electrophysiological characterisation of Scnn1a and Grik4 DREADD RGCs



Courtesy of Gerrit Hilgen

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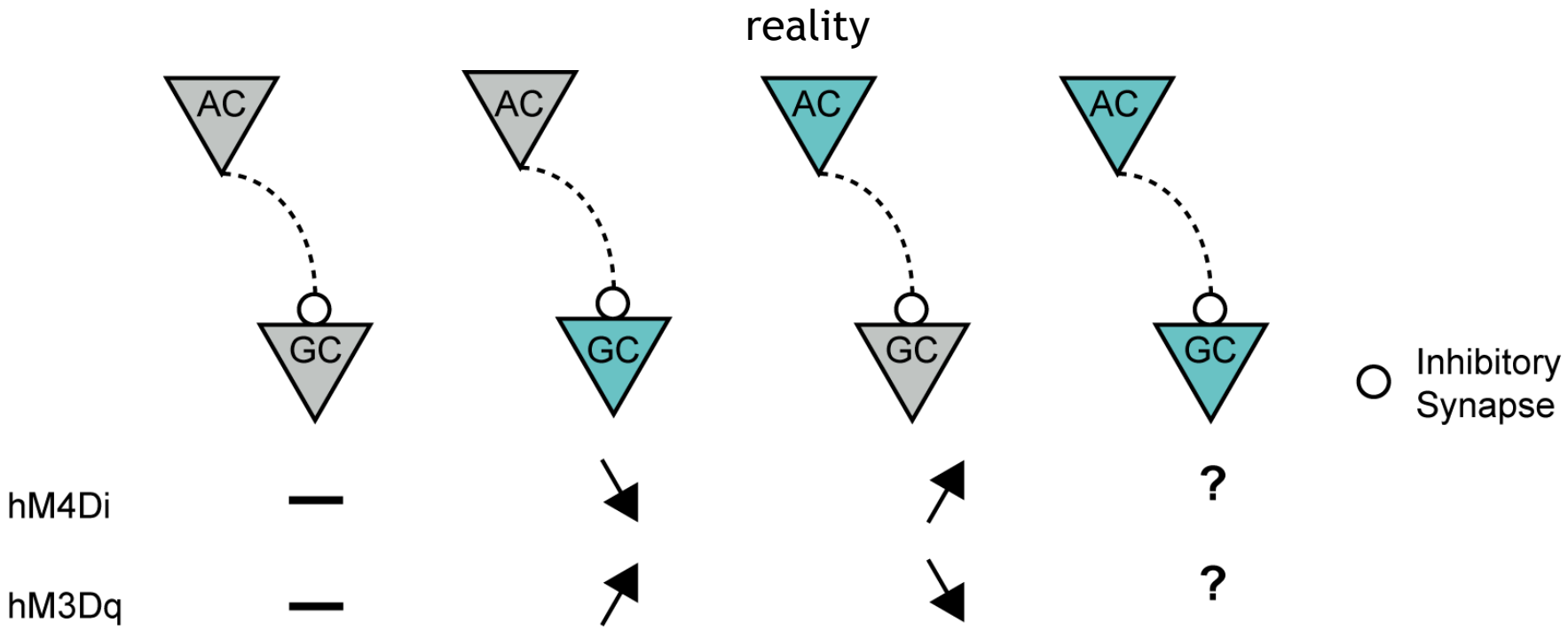
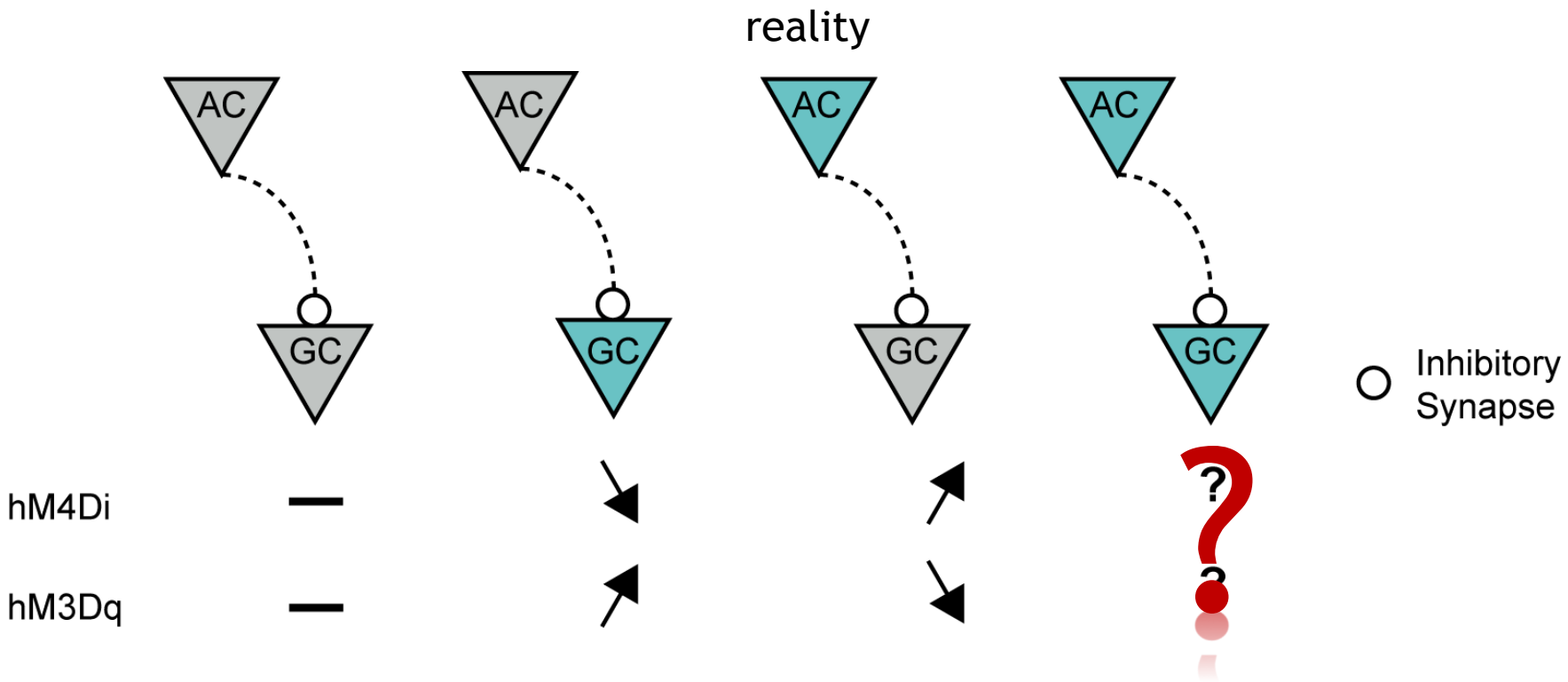


DREADDs in ACs makes the interpretation of functional results from DREADD-expressing RGCs more challenging.

Courtesy of Gerrit Hilgen

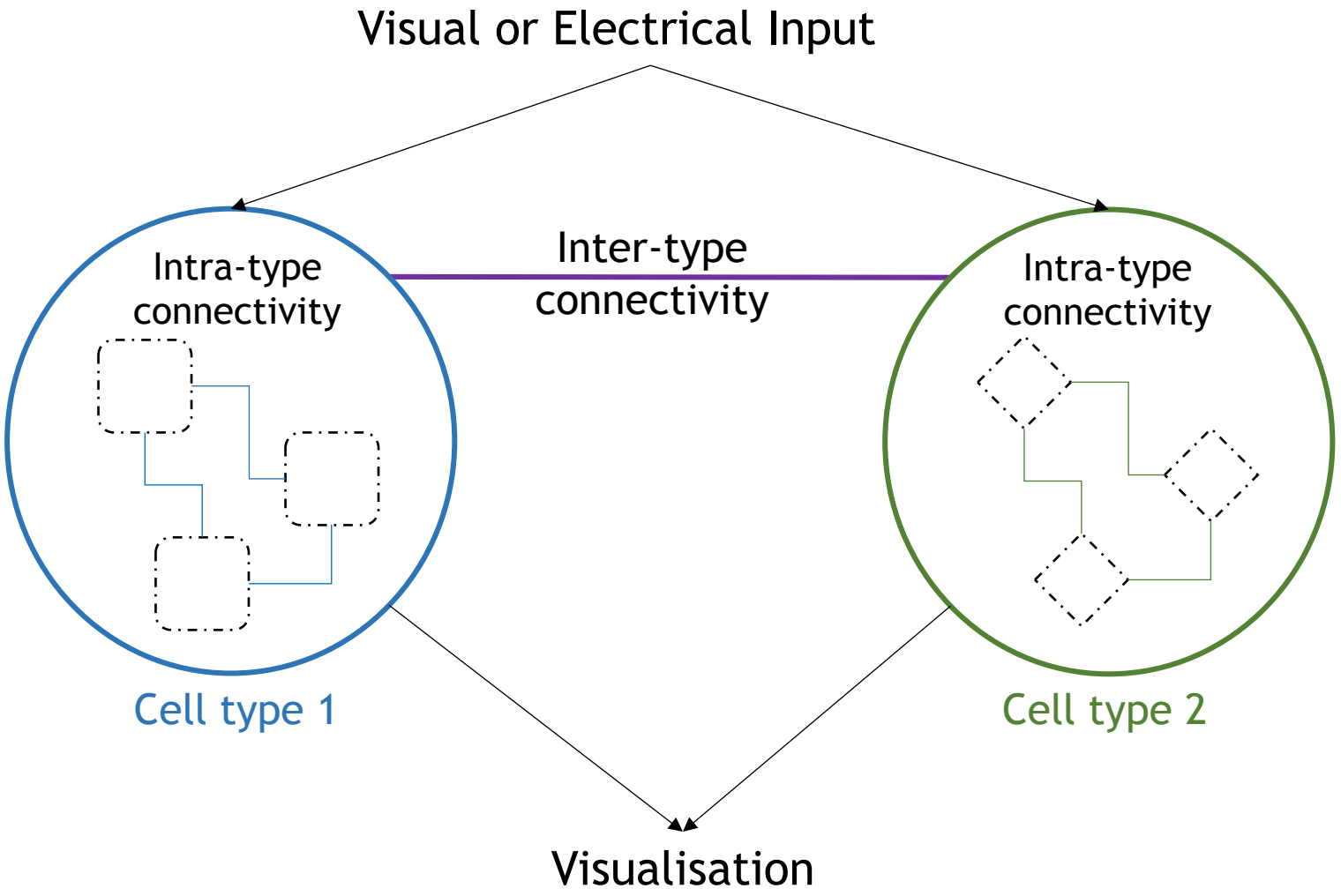
Electrophysiological characterisation of Scnn1a and Grik4 DREADD RGCs

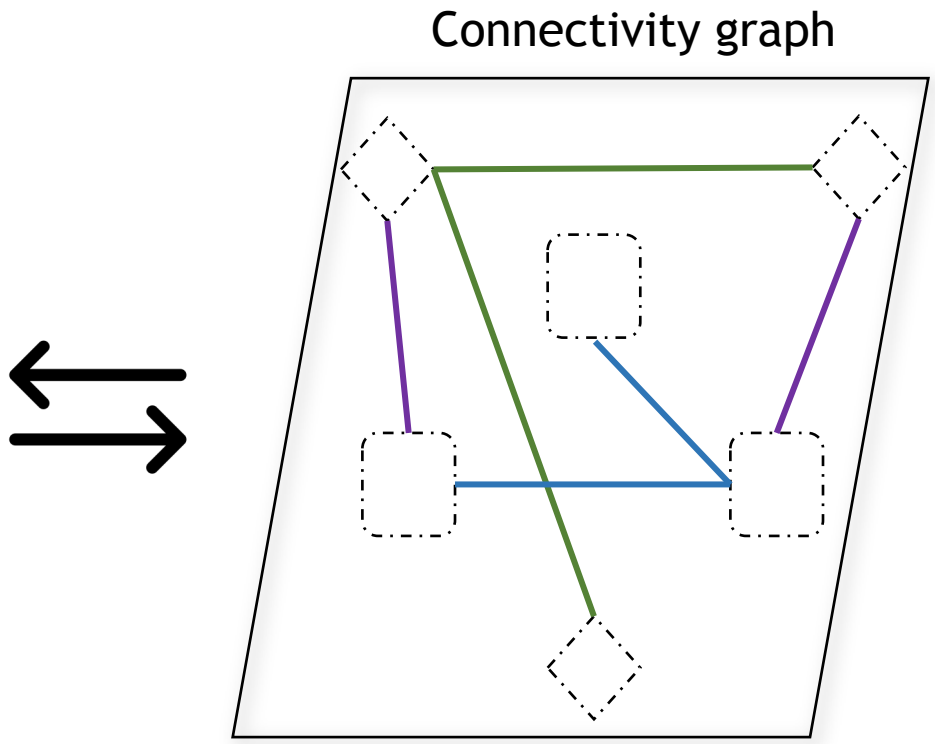


Solution: Study it numerically

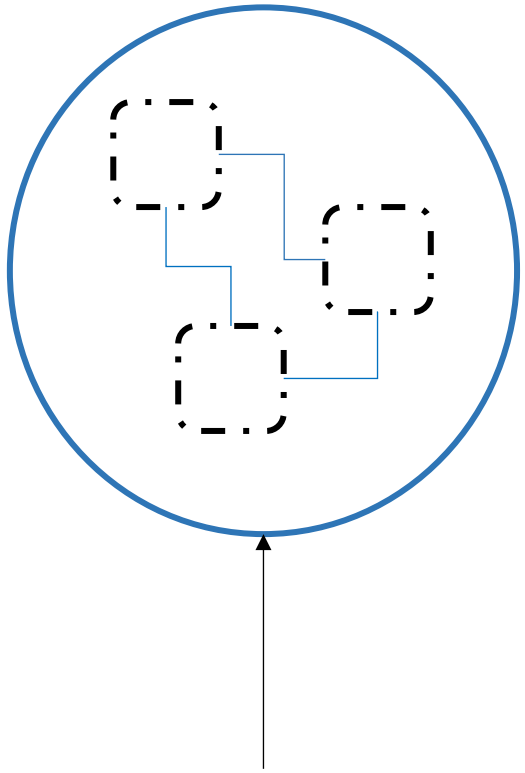
Courtesy of Gerrit Hilgen

General structure



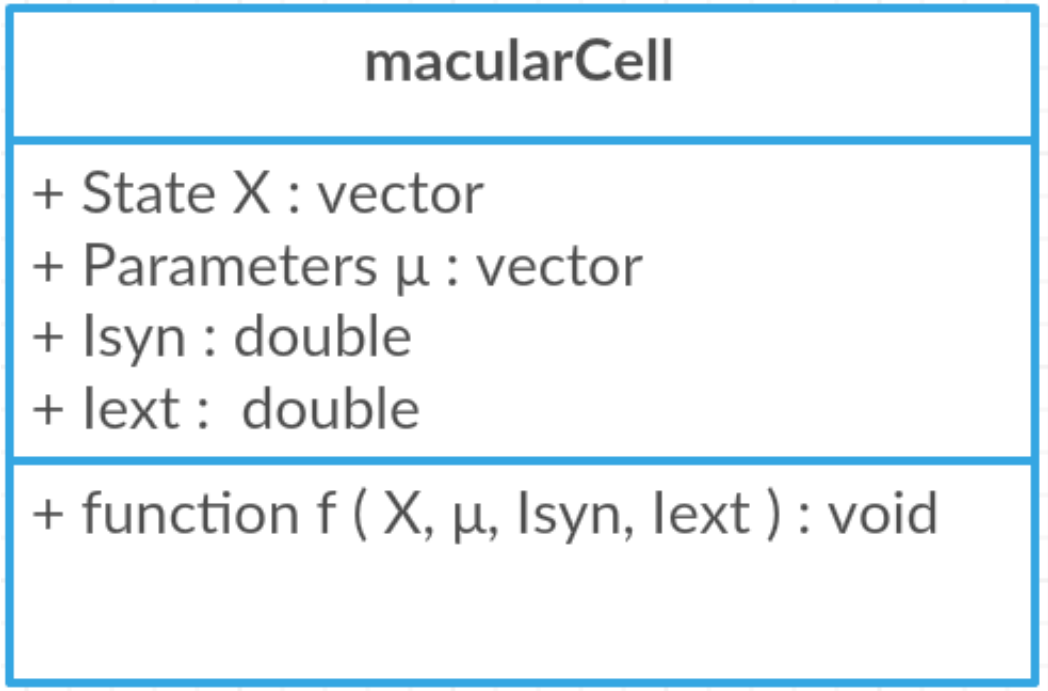


Basic building blocks - cell



Cell

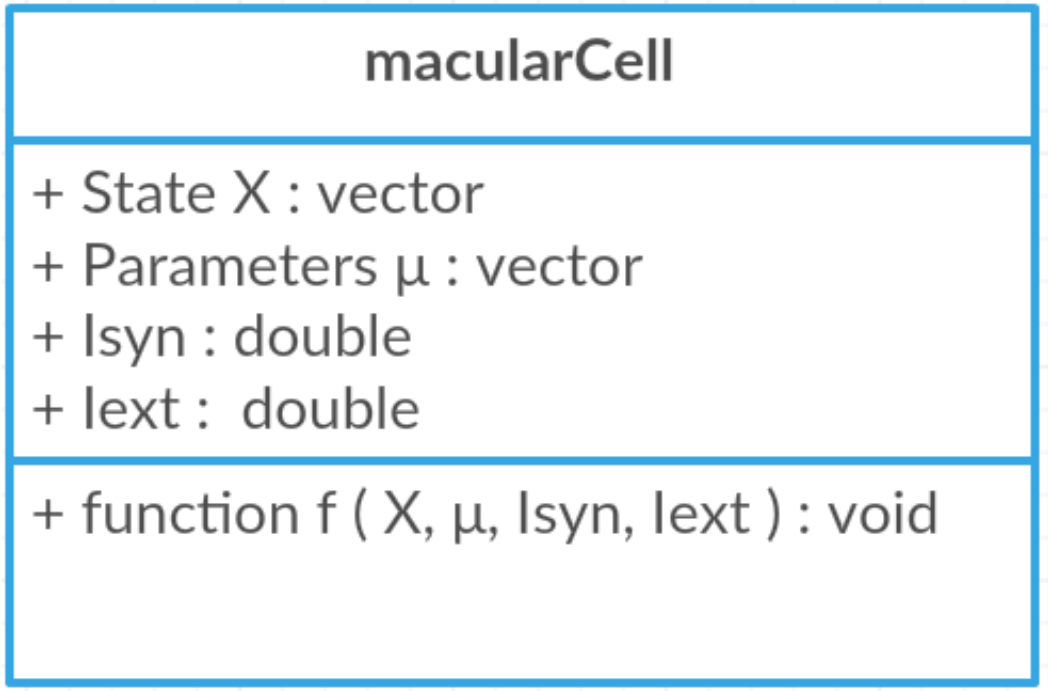
- ✓ A set of **variables** evolving in time and characterizing the cell's evolution : e.g. membrane potential, probability that a ionic channel of a given type is open etc.



Cell

- ✓ A set of **variables** evolving in time and characterizing the cell's evolution : e.g. membrane potential, probability that a ionic channel of a given type is open etc.

- ✓ A set of **parameters** that constrain the cell's evolution : e.g. conductance, reversal potential, membrane capacitance, characteristic time of a channel's activity



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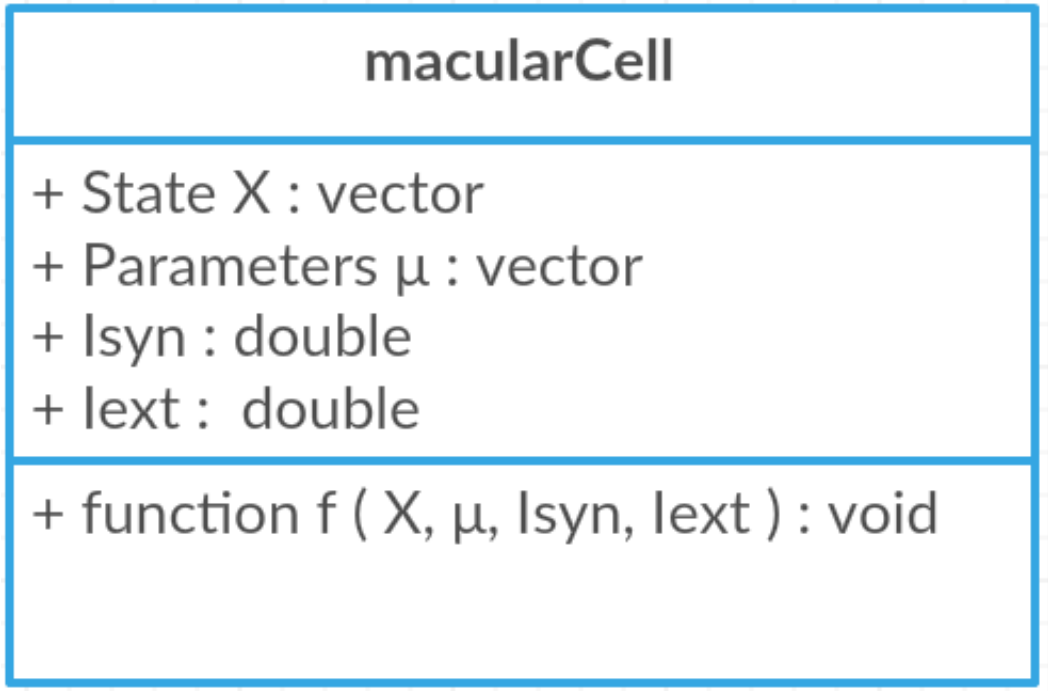
- ✓ A set of **parameters** that constrain the cell's evolution : e.g. conductance, reversal potential, membrane capacitance, characteristic time of a channel's activity
- ✓ A function controlling the cell's evolution with a differential equation



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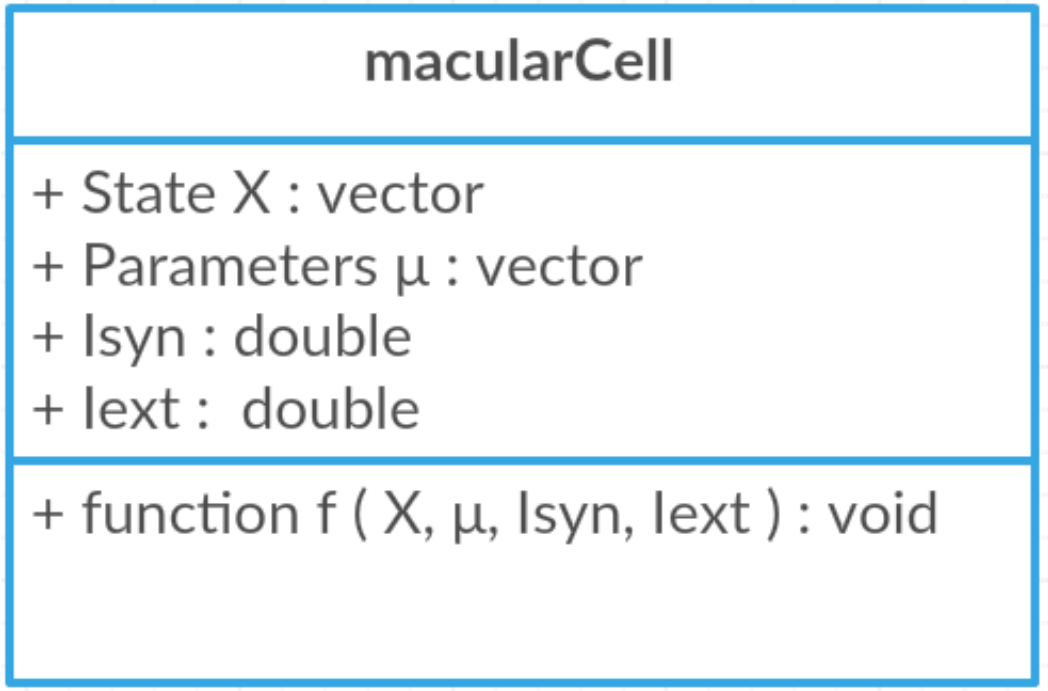
- ✓ A function controlling the cell's evolution
- ✓ **Isyn** : A synaptic input corresponding to synaptic connections with other cells



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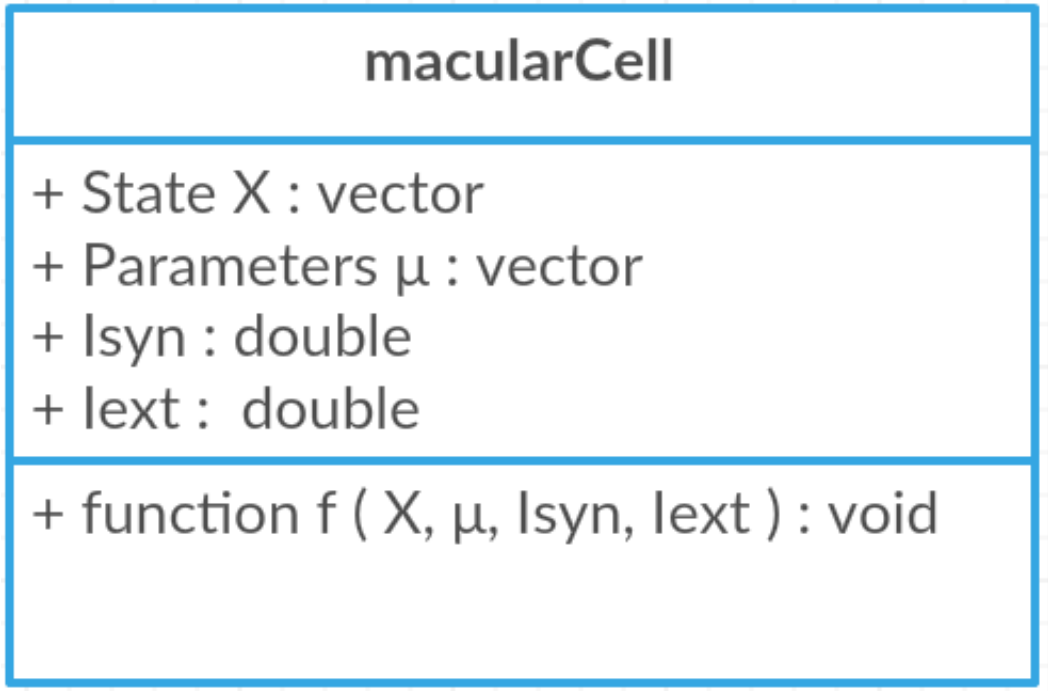
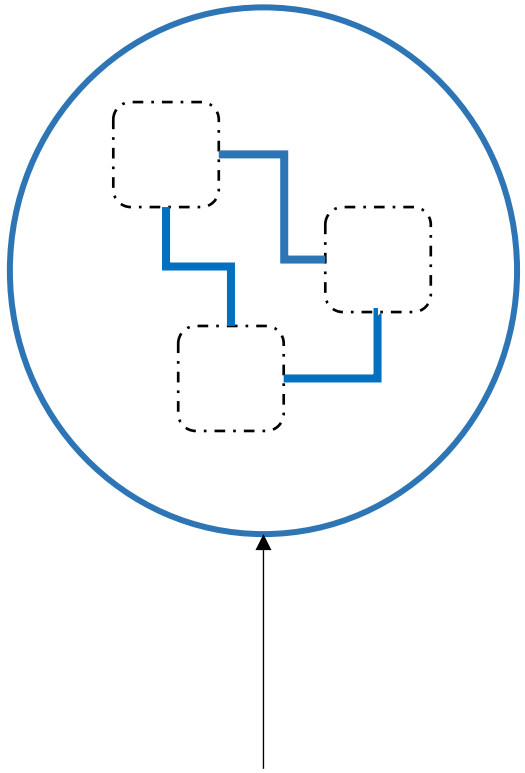
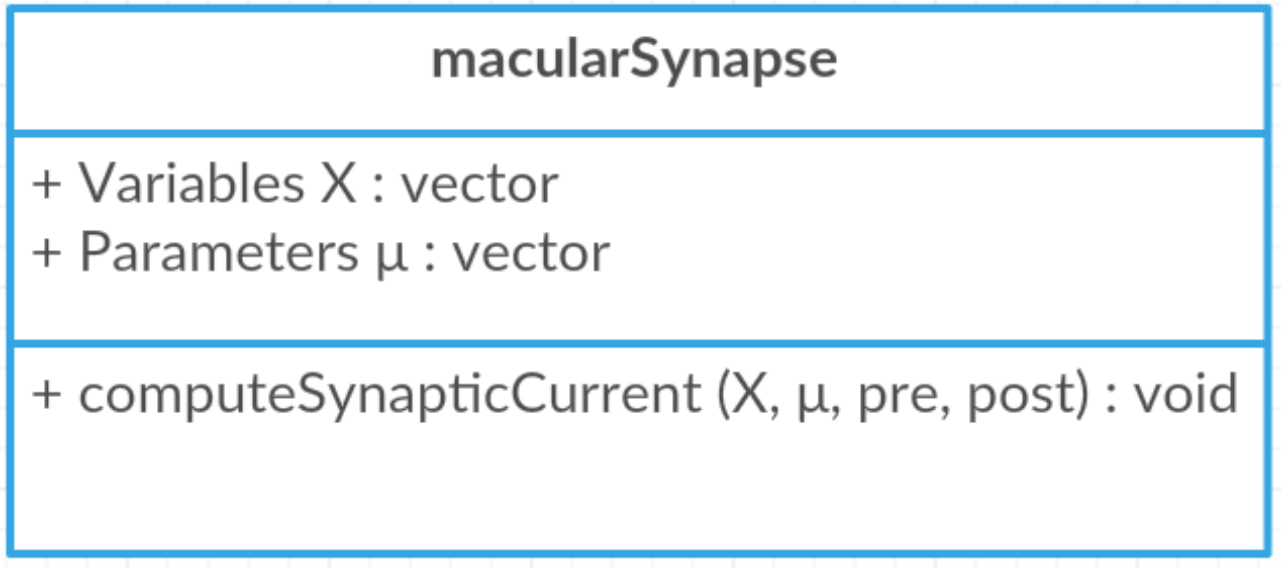
- ✓ A function controlling the cell's evolution
- ✓ **Isyn** : A synaptic input corresponding to synaptic connections with other cells
- ✓ **Iext** : An external input corresponding either to a visual input or the electric current provided by an electrode



Basic building blocks - synapse

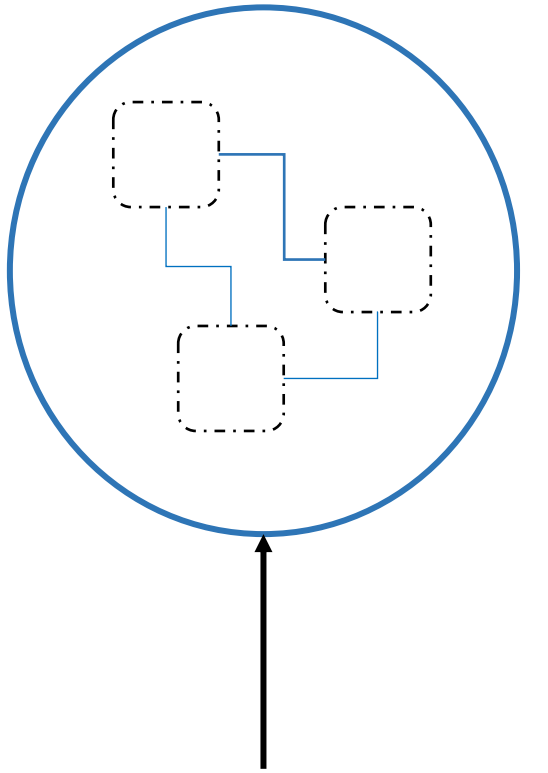


Synapse



- ✓ Chemical or electrical (gap junction)
- ✓ A set of variables that evolve in time : e.g. conductance
- ✓ A set of parameters : e.g. synaptic weight

Basic building blocks – External Input



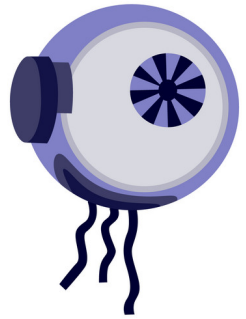
External Input

Visual Input

Virtual Retina module

- ✓ Emulate the outer plexiform layer (OPL) current

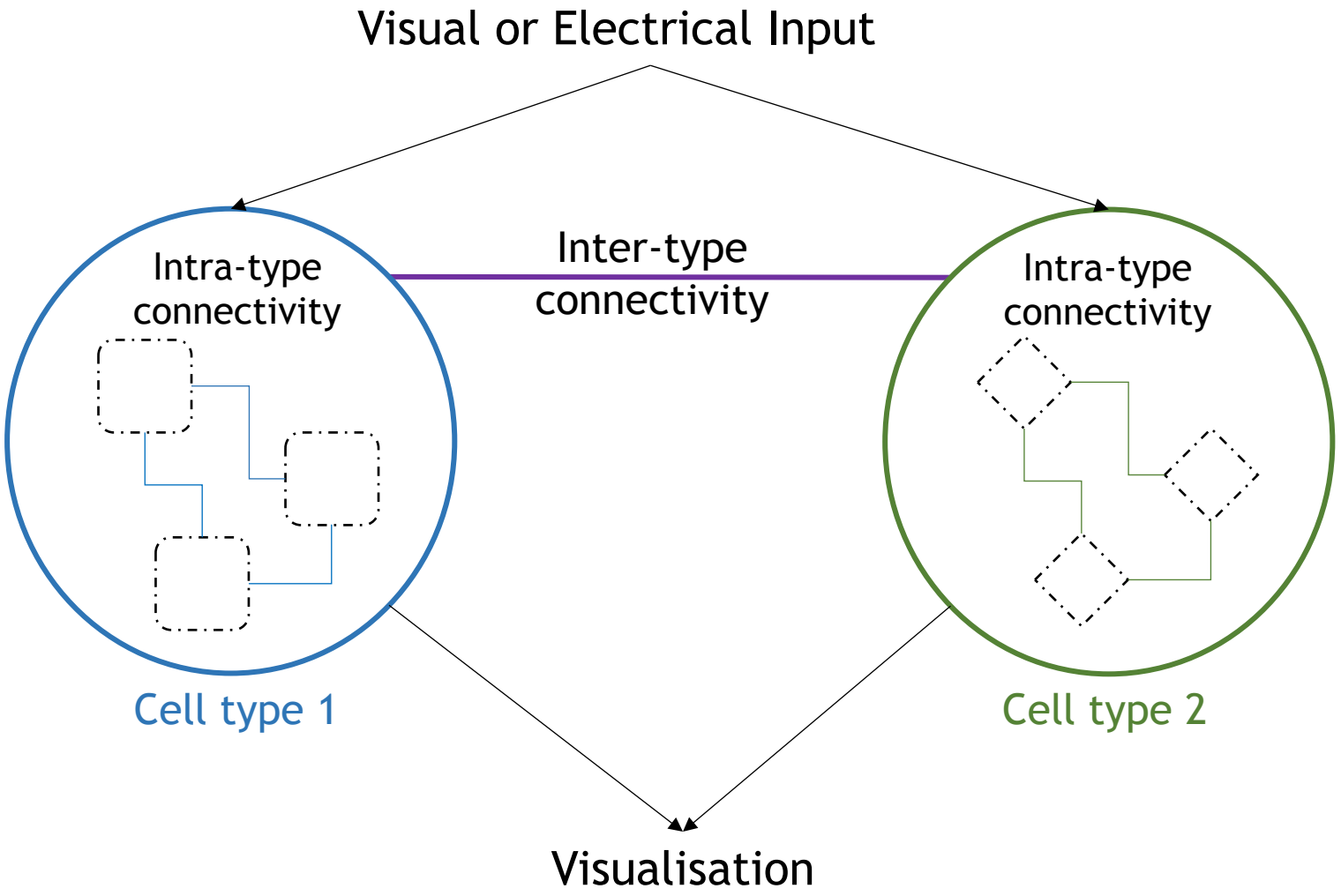
A.Wohrer et al., 2009

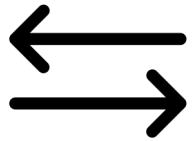


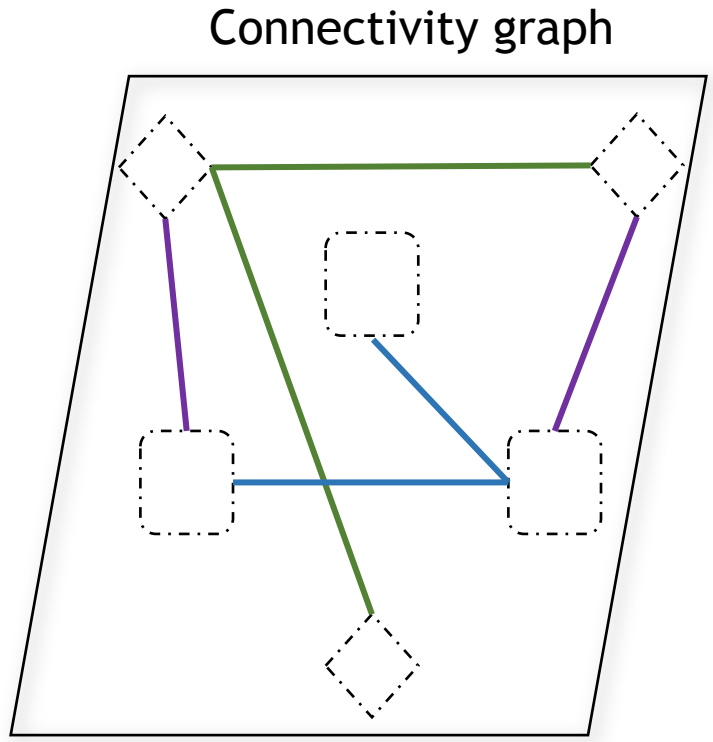
Retinal prosthesis

- ✓ Emulate the electric current provided by an electrode

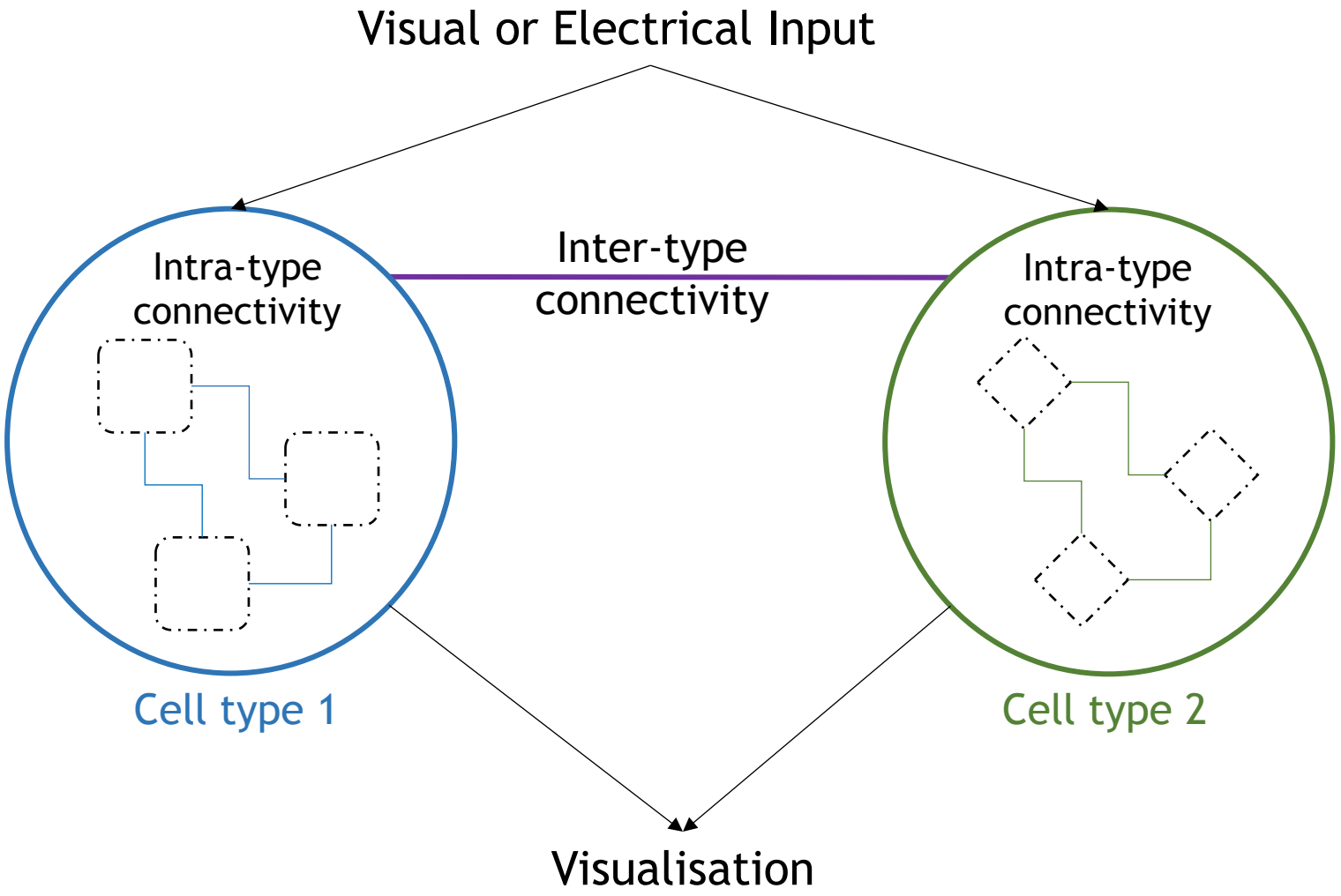
General structure

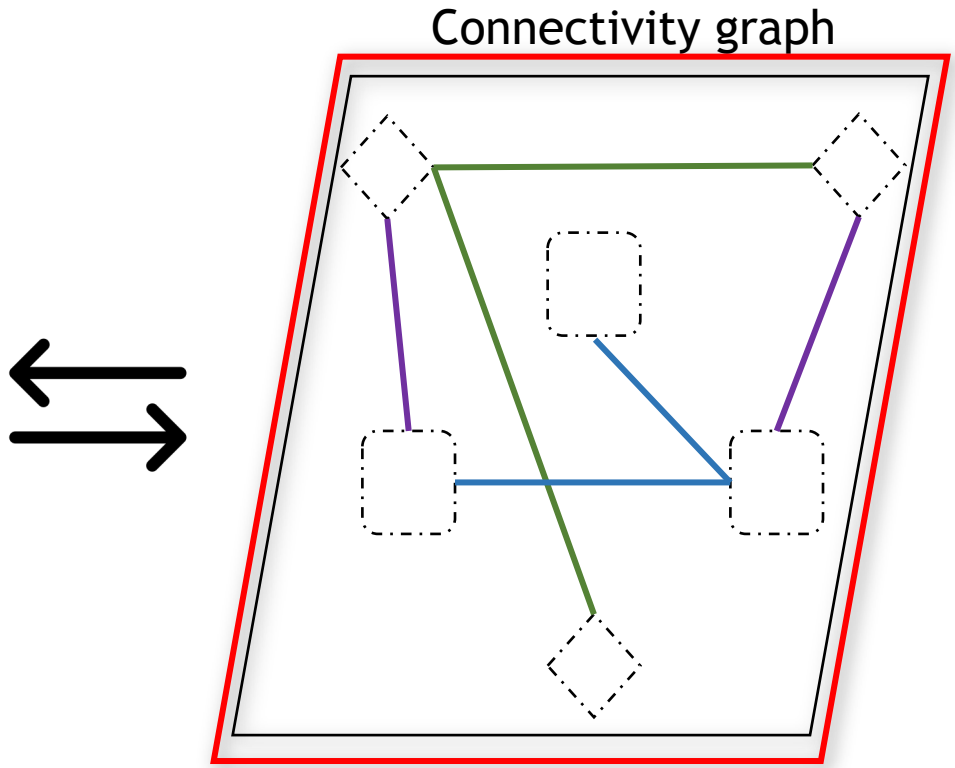




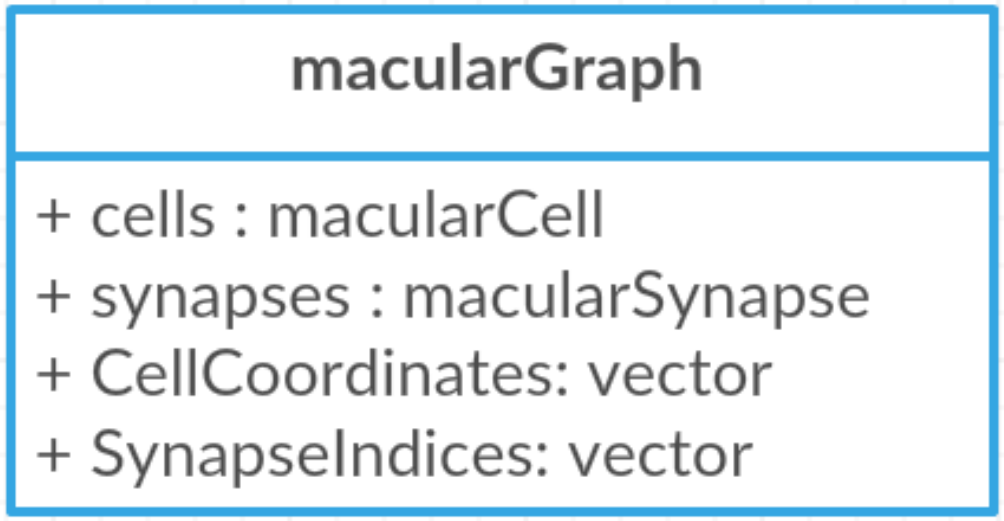


General structure



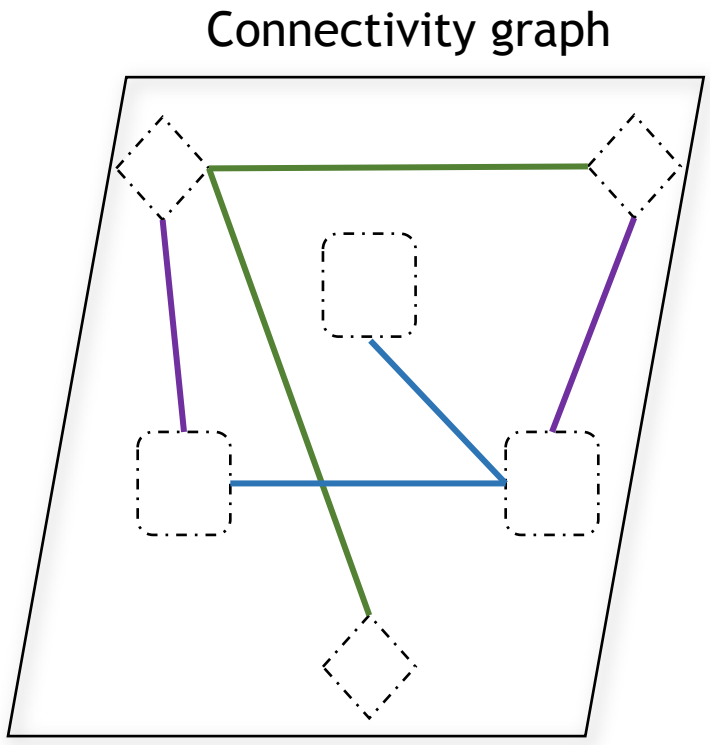


Graph

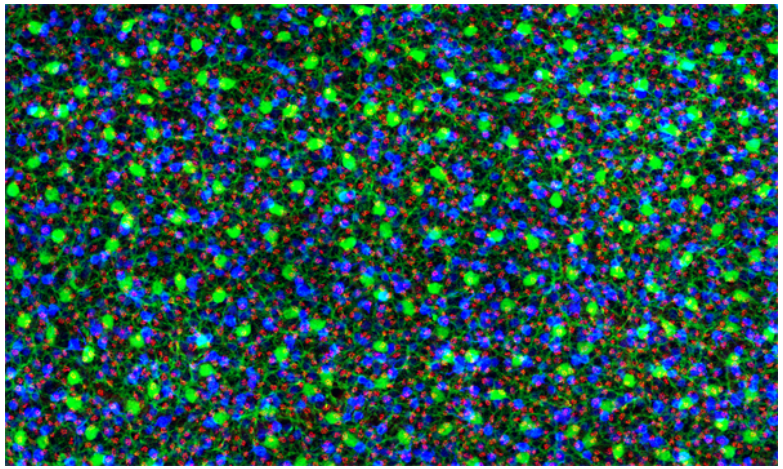


- ✓ Cell types
- ✓ Synapse types
- ✓ Cell coordinates
- ✓ Synapse indices

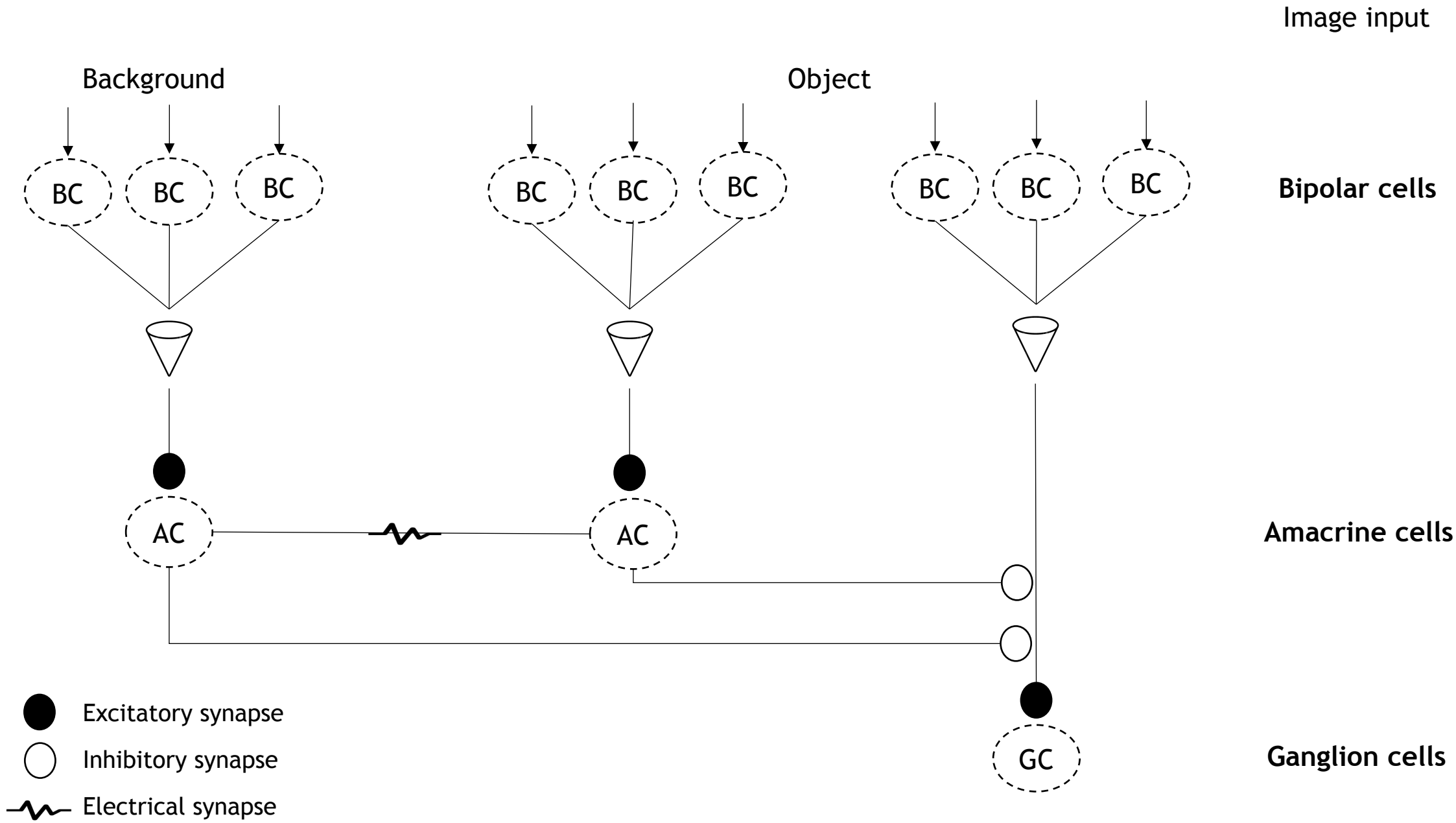
Graph



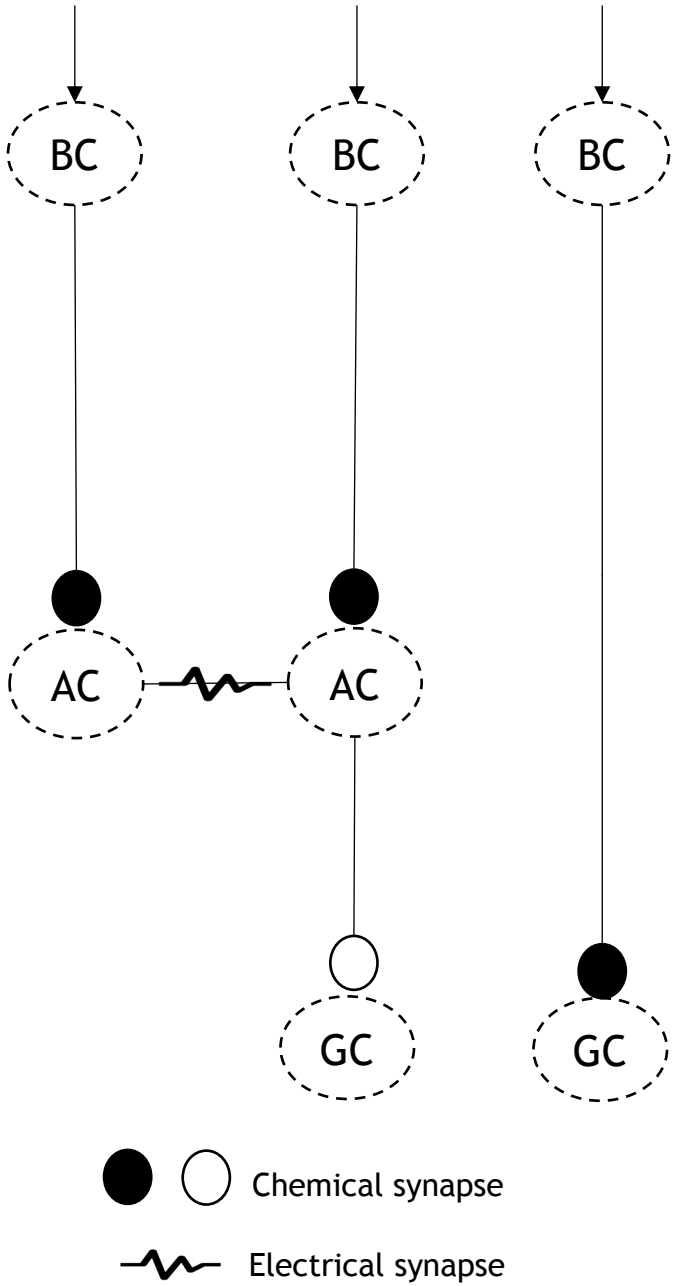
- ☞ Design a local circuit with specific connectivity patterns
- ☞ Deploy it to the whole retina

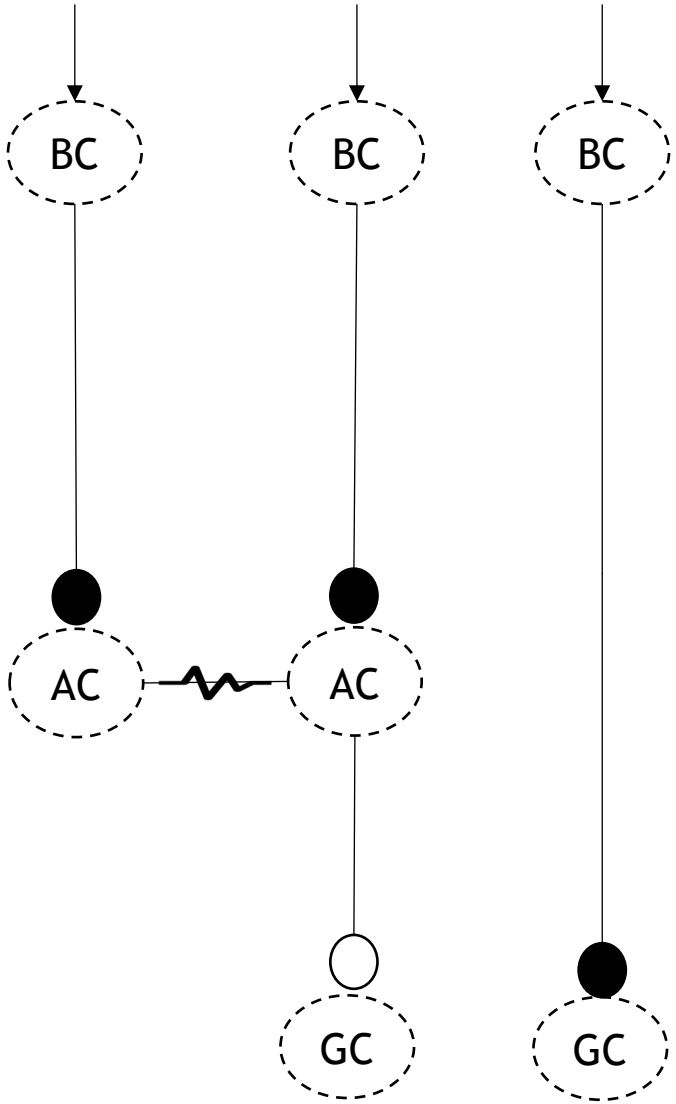


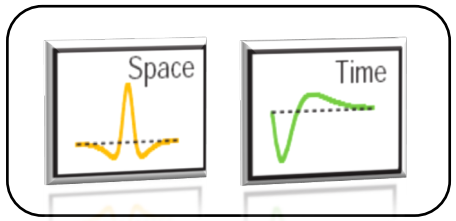
Source: *From Gabriel Luna, Steve Fisher and Geoff Lewis, retinal cell biology group at UC Santa Barbara Neuroscience Research Institute*



Inspired from Baccus et al., 2008

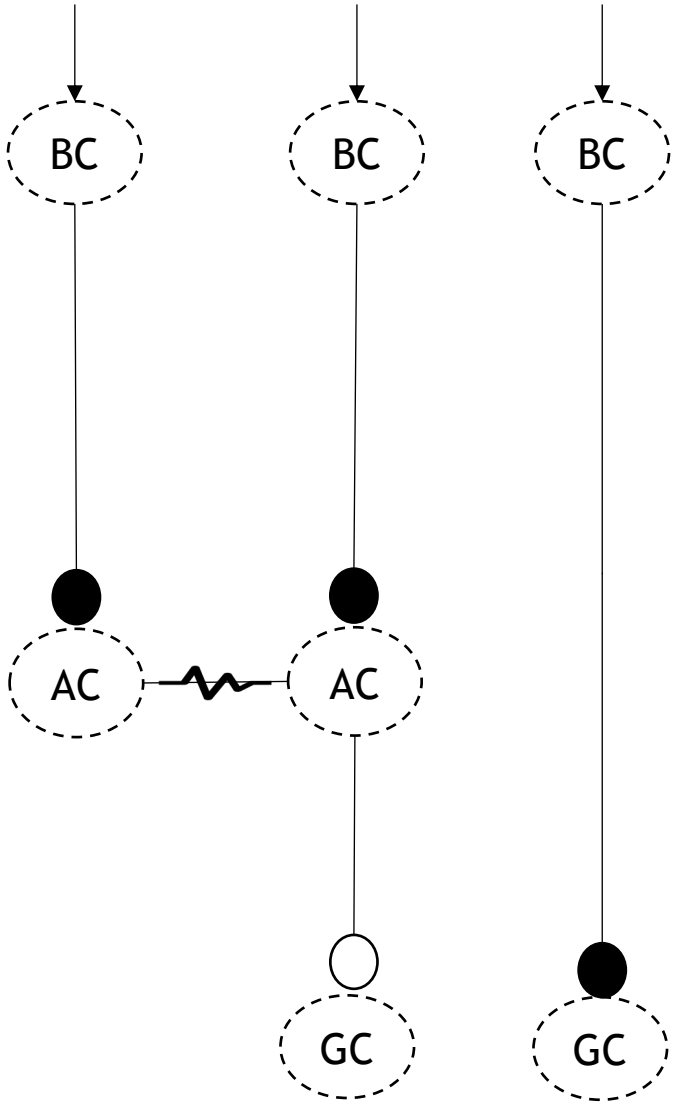

BC
BC
BC
AC
AC
GC
GC
Chemical synapse
Electrical synapse

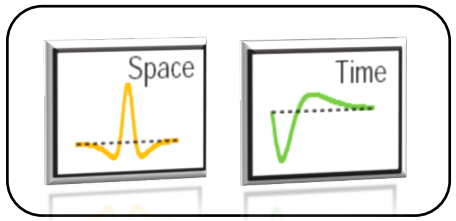




$$K(x, y, t) = K_S(x, y)K_T(t)$$

$$\int (S * \mathrm{K})(\mathrm{x,y,t})$$





Chemical synapse

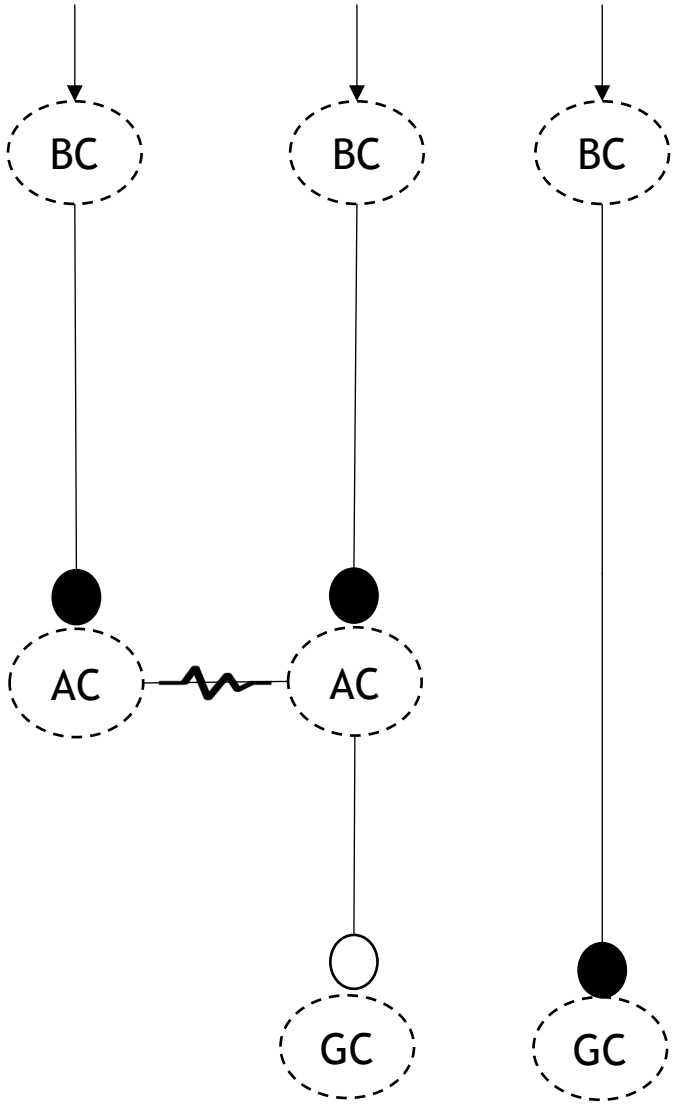
Electrical synapse

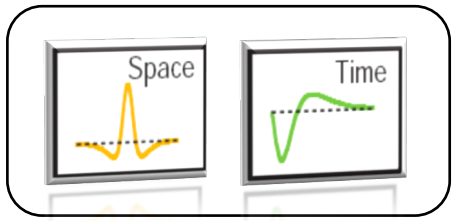
$$K(x,y,t) = K_S(x,y)K_T(t)$$

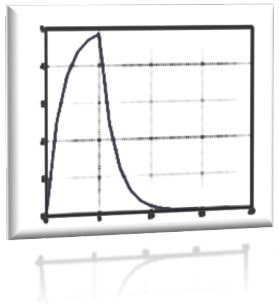
$$\int (S * \mathrm{K})(\mathrm{x,y,t})$$

$$I_{syn} = -g_{syn}\left(V_{post} - E_{syn}\right)$$

$$I_{GAP} = -g_{GAP}\left(V_{post} - V_{pre}\right)$$







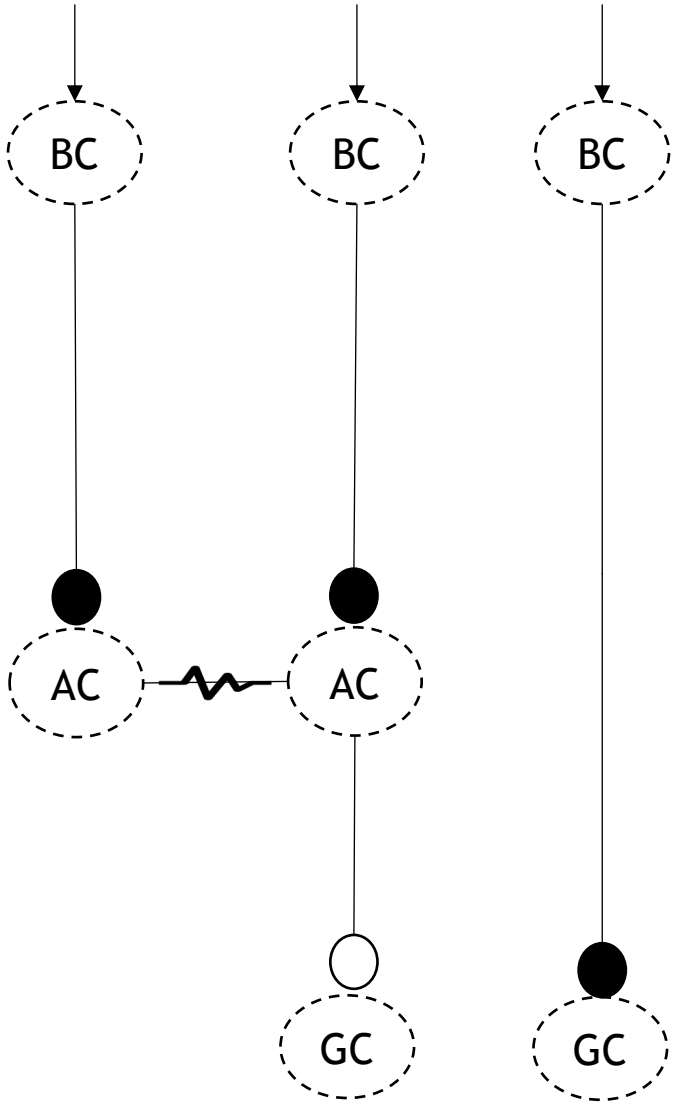
$$K(x,y,t) = K_S(x,y)K_T(t)$$

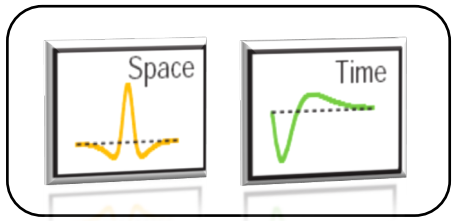
$$\int (S * \mathrm{K})(\mathrm{x,y,t})$$

$$I_{syn} = -g_{syn}\left(V_{post} - E_{syn}\right)$$

$$I_{GAP} = -g_{GAP}\left(V_{post} - V_{pre}\right)$$

$$C\frac{dV}{dt} = -g_L(V - V_L) + Isyn + Iext + I_{CNO}$$



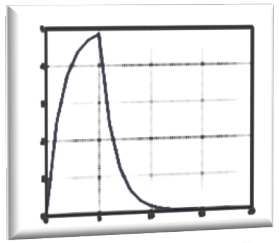


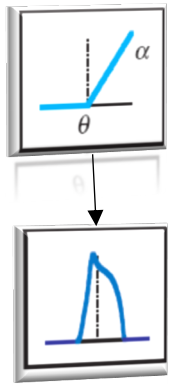
$$K(x,y,t) = K_S(x,y)K_T(t)$$

$$\int (S * \mathrm{K})(\mathrm{x,y,t})$$

$$I_{syn} = -g_{syn}\left(V_{post} - E_{syn}\right)$$

$$I_{GAP} = -g_{GAP}\left(V_{post} - V_{pre}\right)$$

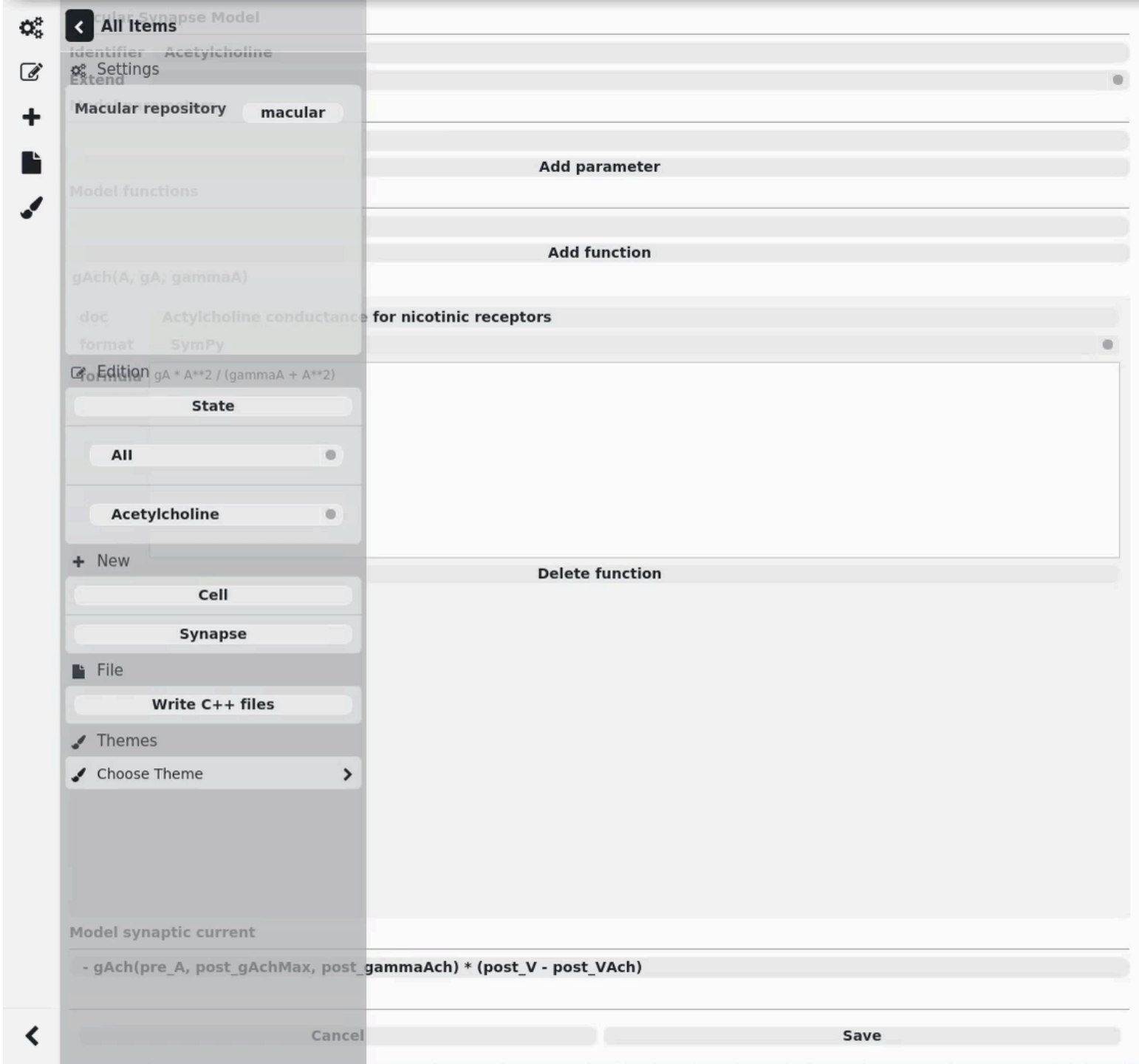


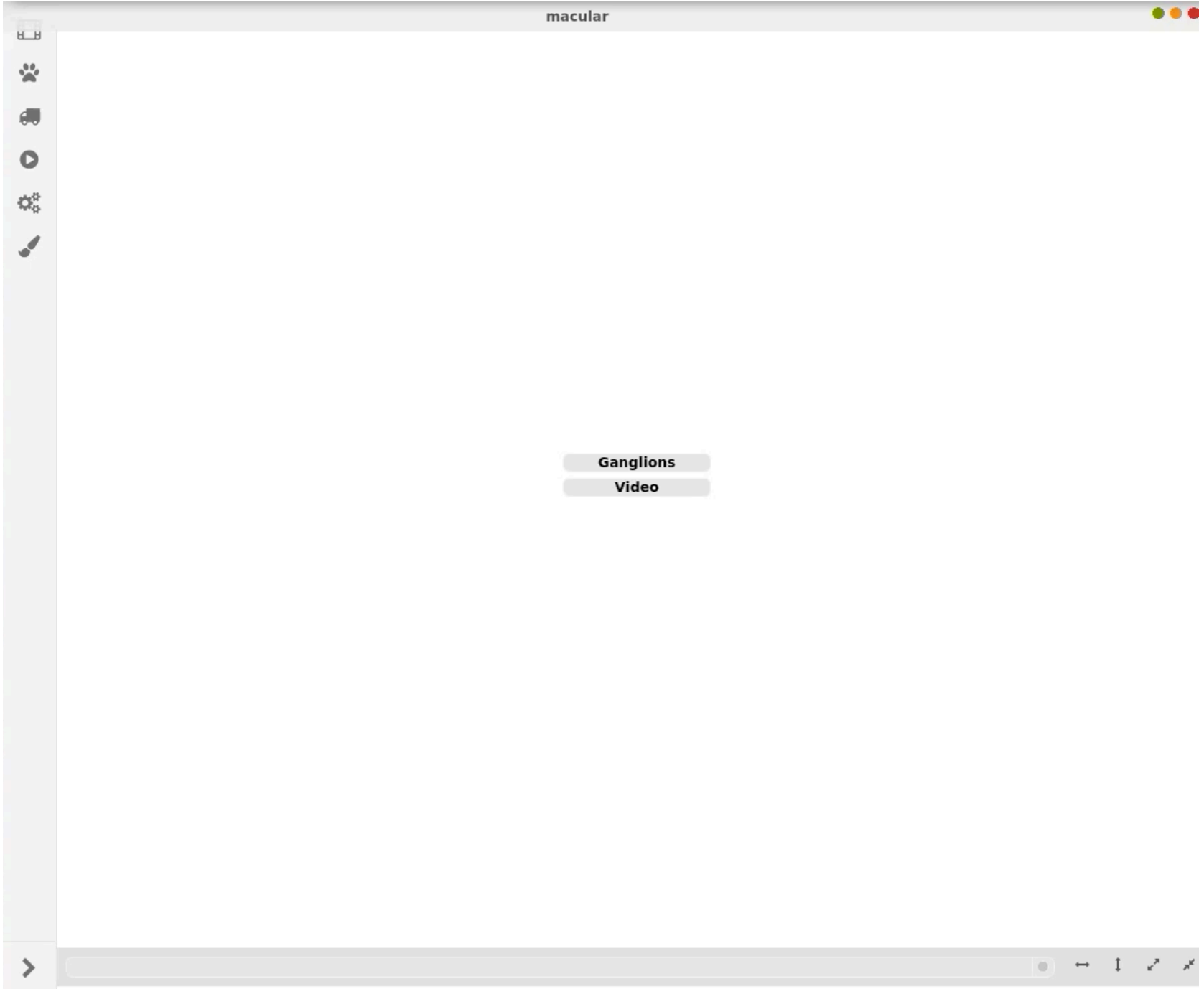


$$C\frac{dV}{dt} = -g_L(V - V_L) + Isyn + Iext + I_{CNO}$$

$$N_G(V) = \begin{cases} 0, & if(V \le 0) \\ \alpha(V-\theta), & if(\theta \le V \le \frac{N_{max}}{\alpha+\theta}) \\ N_{max}, & otherwise \end{cases}$$

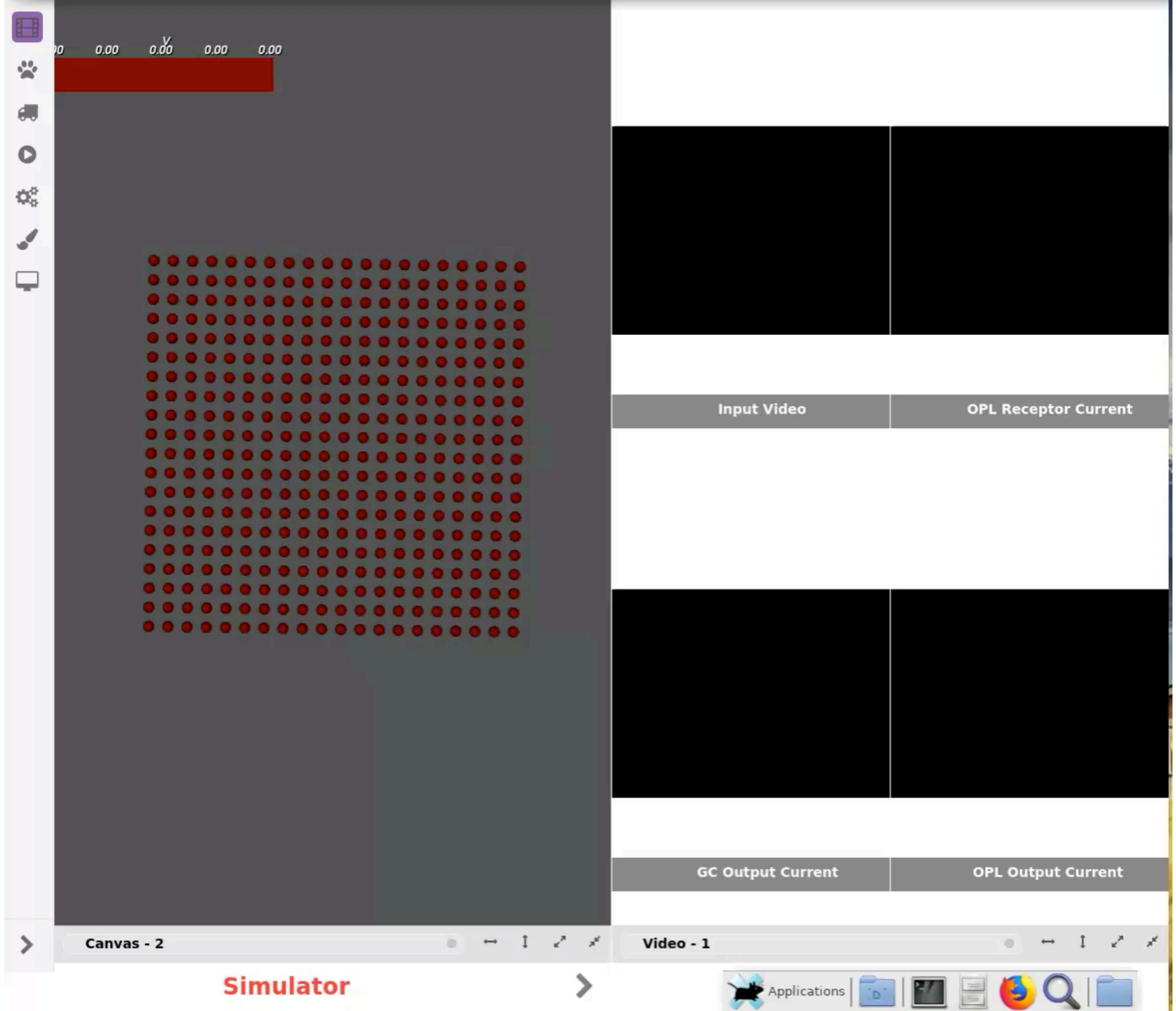
Chen et al., Journal of Neuroscience 2 January 2013


All Items
Settings
Macular repository
macular
Edition
State
All
Acetylcholine
New
Cell
Synapse
File
Write C++ files
Themes
Choose Theme
Add parameter
Add function
Delete function
for nicotinic receptors
Model synaptic current
- gAch(pre_A, post_gAchMax, post_gammaAch) * (post_V - post_VAch)
Cancel
Save



Simulator

Graph Generator


0.00
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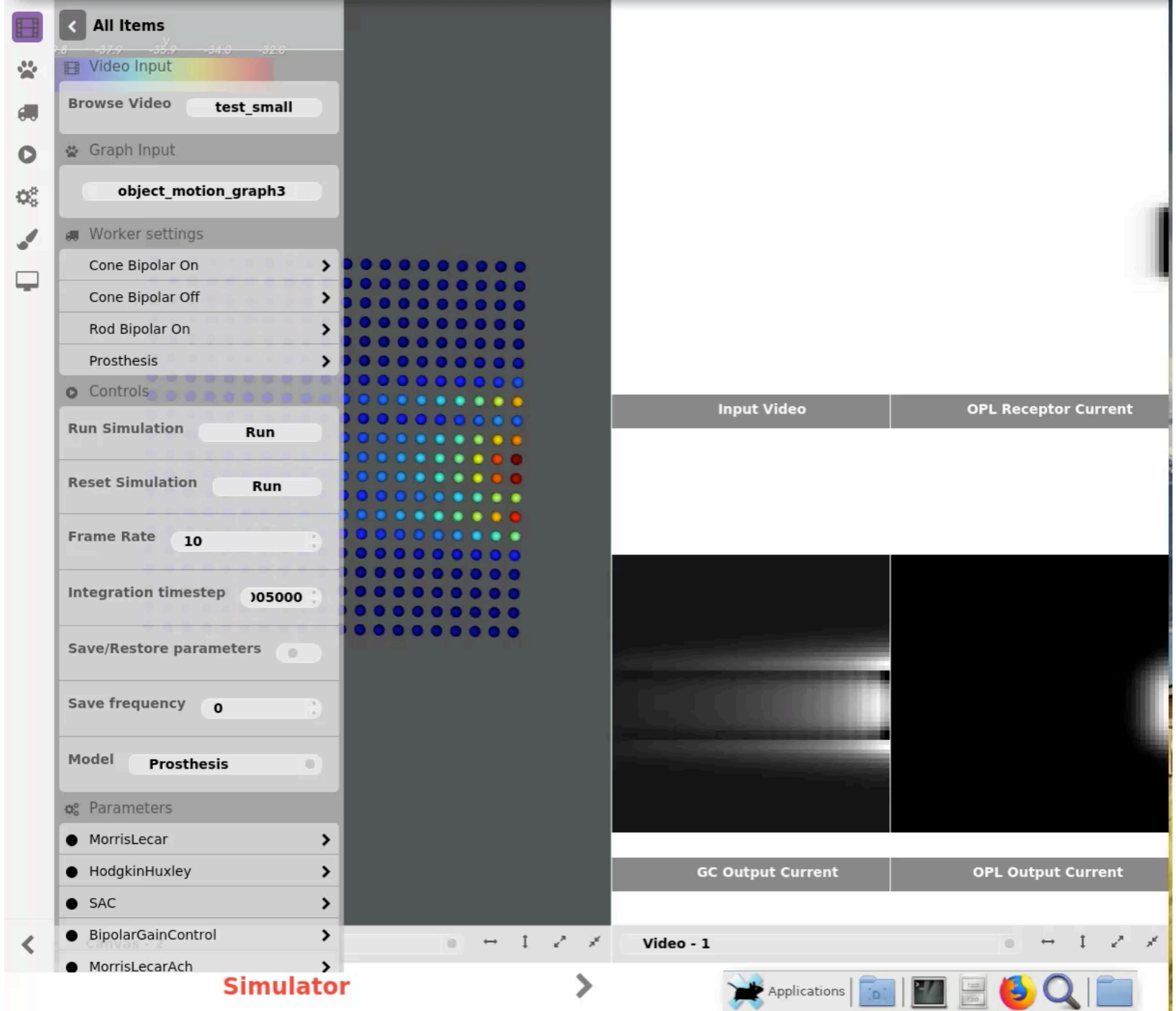
0.00
0.00
Input Video
OPL Receptor Current
GC Output Current
OPL Output Current
Canvas - 2
Video - 1
Simulator
Applications


All Items
Video Input
Browse Video
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Graph Input
object_motion_graph3
Worker settings
Cone Bipolar On
Cone Bipolar Off
Rod Bipolar On
Prosthesis
Controls
Run Simulation
Run
Reset Simulation
Run
Frame Rate
10
Integration timestep
Save/Restore parameters
Save frequency
0
Model
Prosthesis
Parameters
MorrisLecar
HodgkinHuxley
SAC
BipolarGainControl
MorrisLecarAch
Input Video
OPL Receptor Current
GC Output Current
OPL Output Current
Video - 1
Applications

Simulator

Thank you!

Questions?