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Probing retinal function with a multi-layered simulator

Evgenia Kartsaki, Bruno Cessac, Gerrit Hilgen, Evelyne Sernagor

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Submitted on 2 Dec 2019

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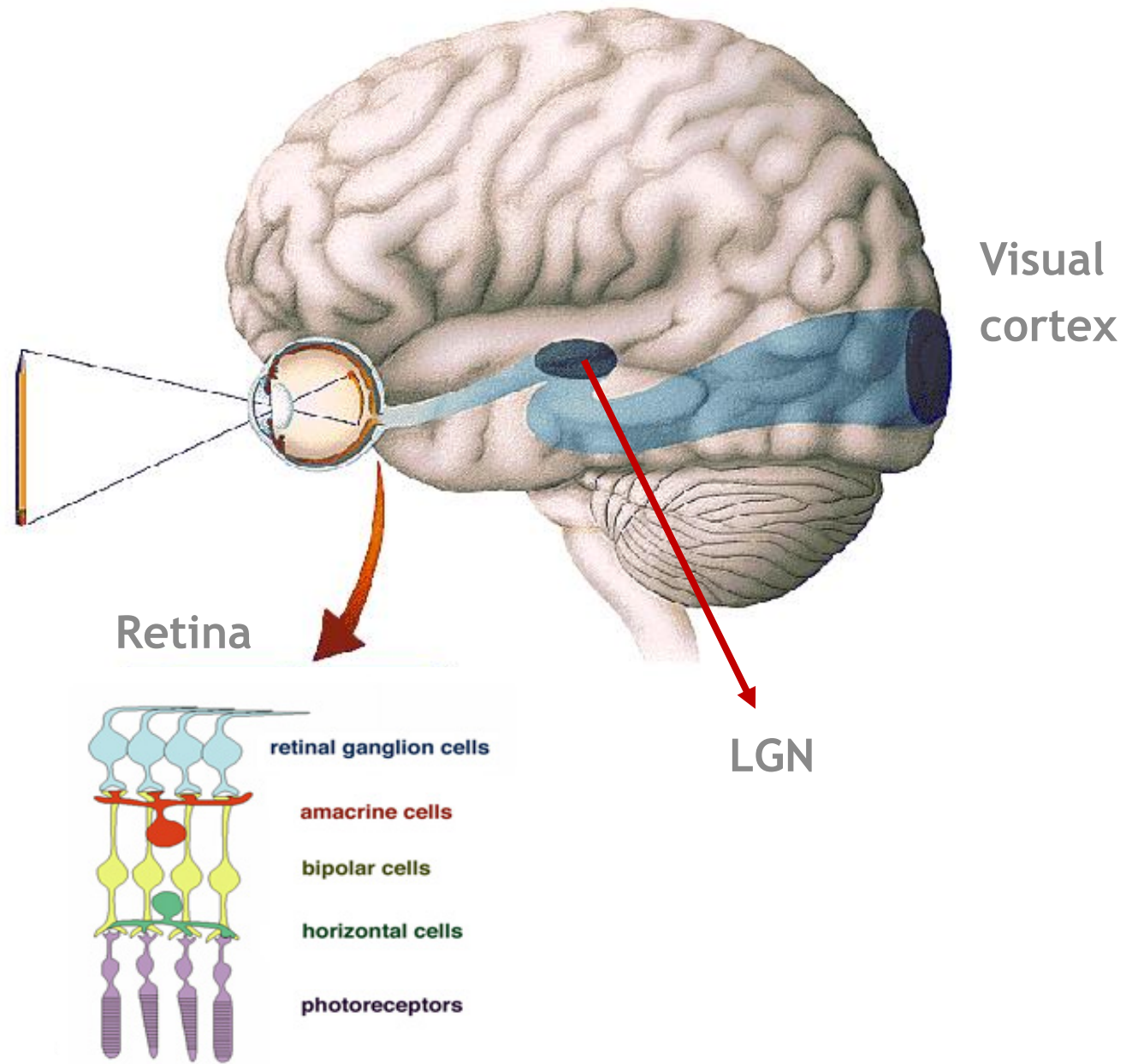


NeuroMod Institute meeting

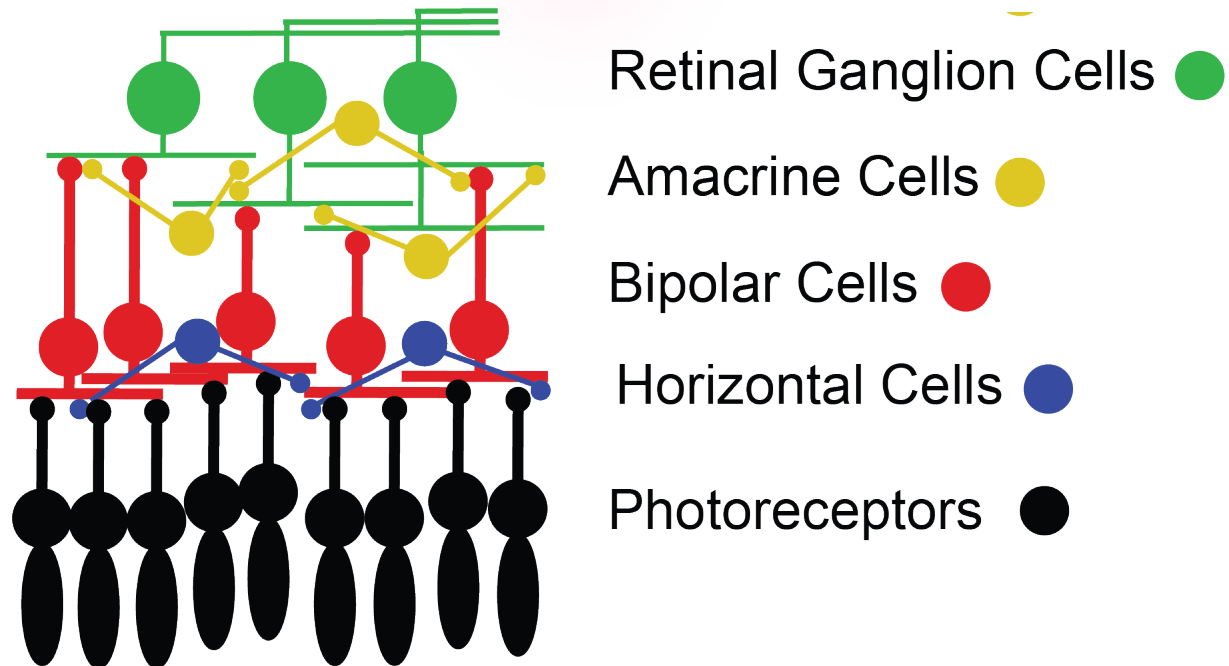
Probing retinal function with a multi-layered simulator

Evgenia Kartsaki^{1,2}, Bruno Cessac¹, Gerrit Hilgen², Evelyne Sernagor²

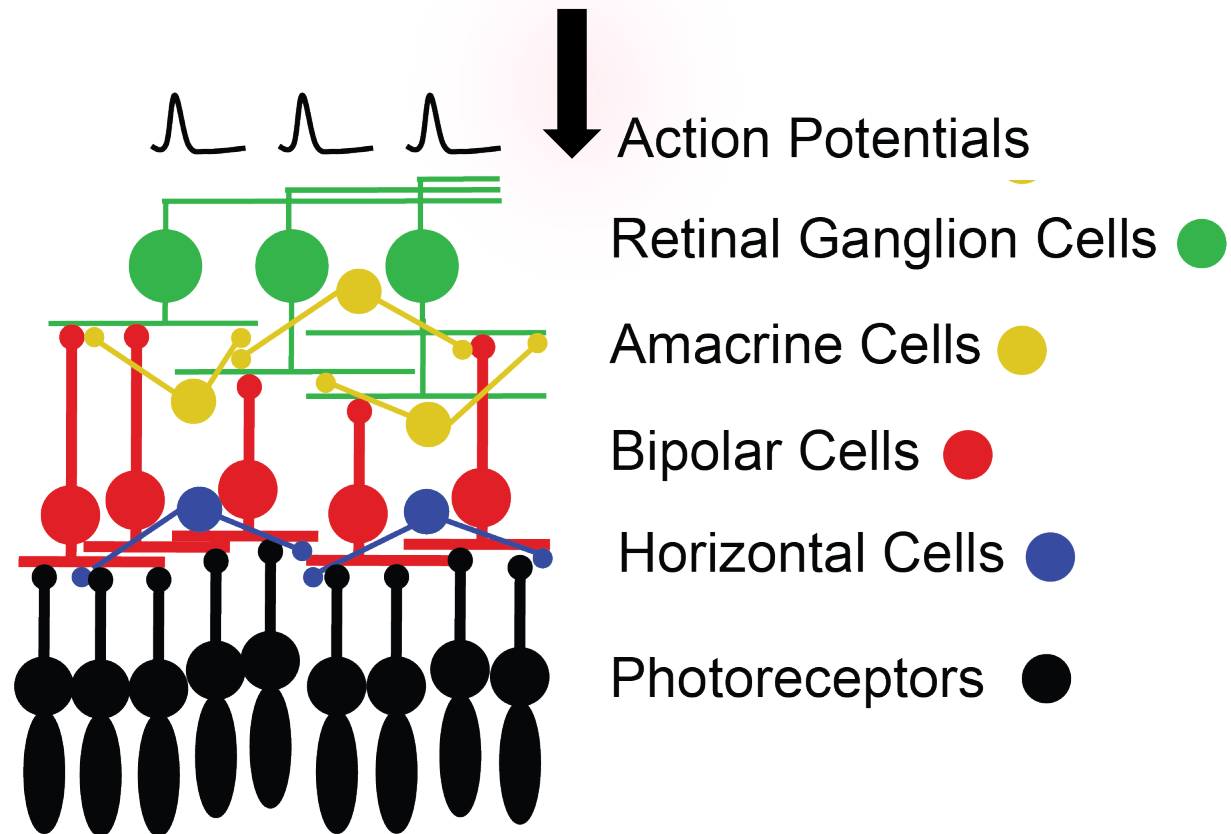
¹Biovision team, Université Côte d'Azur, Inria, France
²Institute of Neuroscience, University of Newcastle, UK



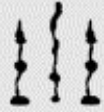
Retinal visual flow



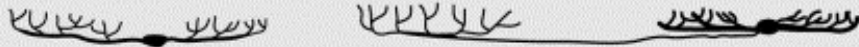
Retinal visual flow



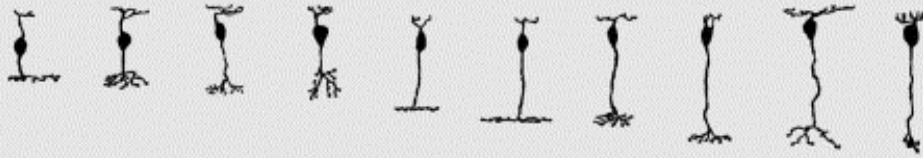
Photoreceptors



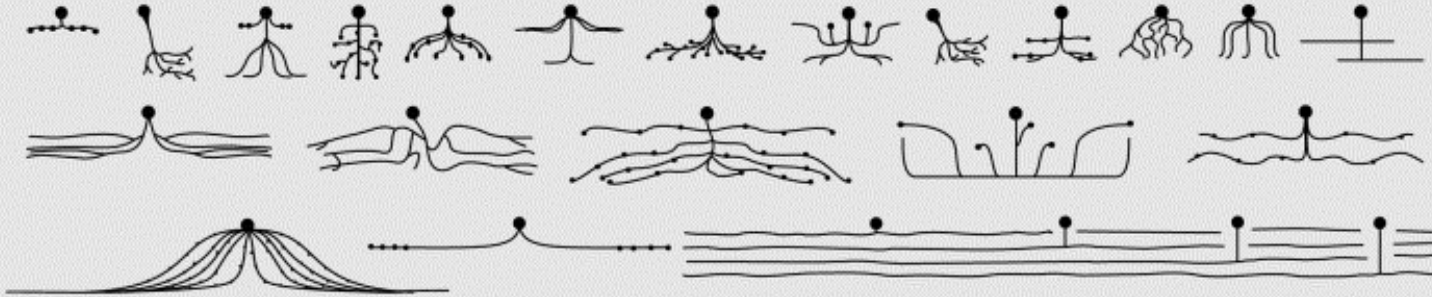
Horizontal cells



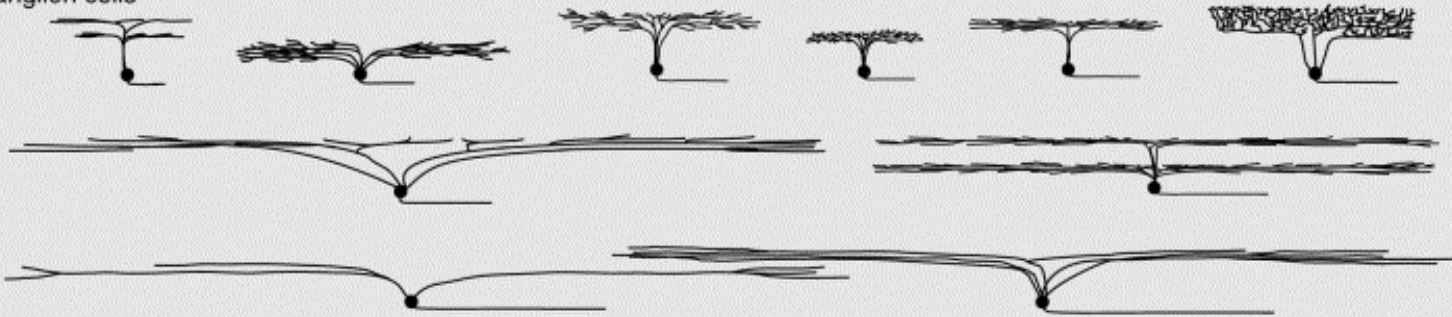
Bipolar cells



Amacrine cells



Ganglion cells



Retinal neurons inventory

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

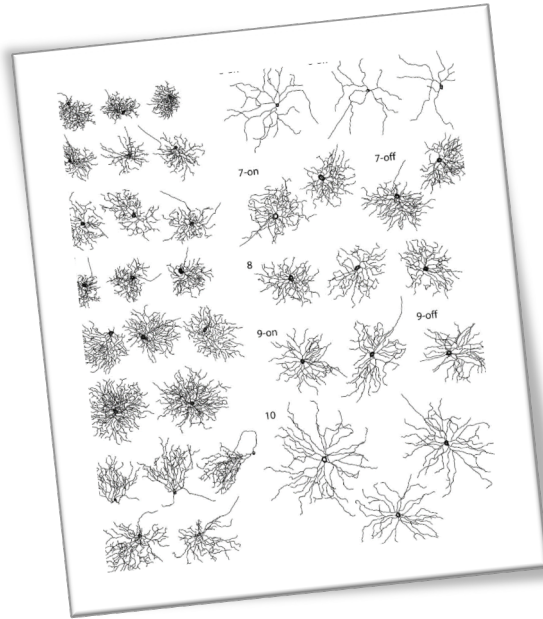
LEVERHULME
TRUST

 **Newcastle**
University
Institute of
Neuroscience

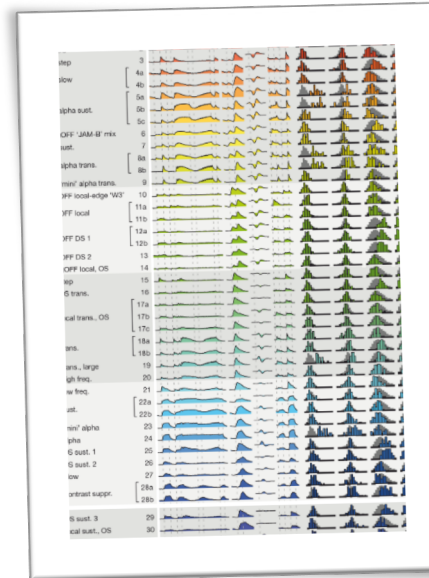
Inria
informatiques mathématiques

UNIVERSITÉ
CÔTE D'AZUR 

Yet another RGC classification...



Coombs et al., 2006



Baden, Berens, Franke et al., 2016

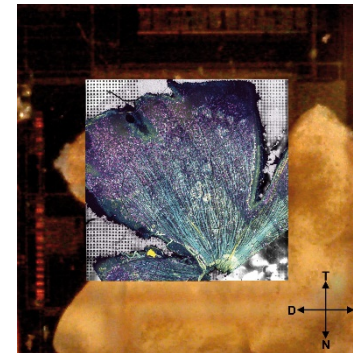
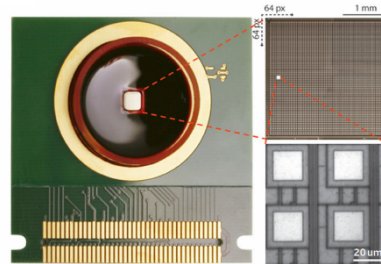
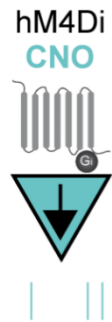


Martersteck, Hirokawa, Everts et al., 2017

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

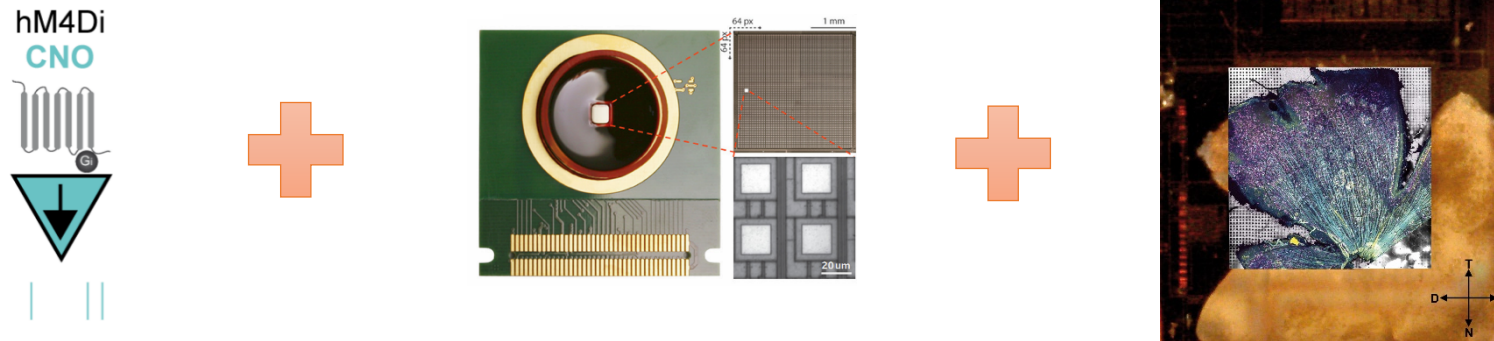
Aims

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



Aims

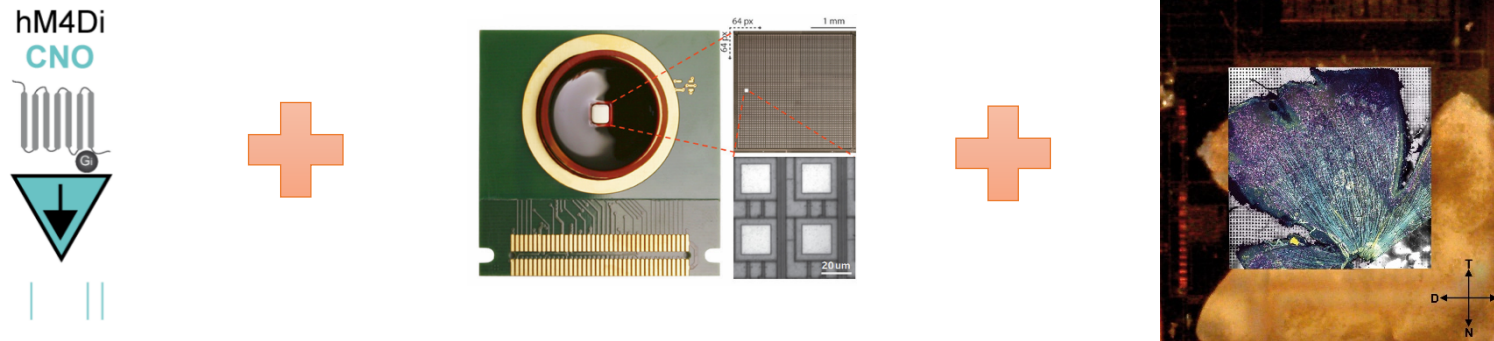
- Identify RGCs sharing a common gene expression by combining *pharmacogenetics*, large-scale high-density *electrophysiology* and *immunohistochemistry*



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

Aims

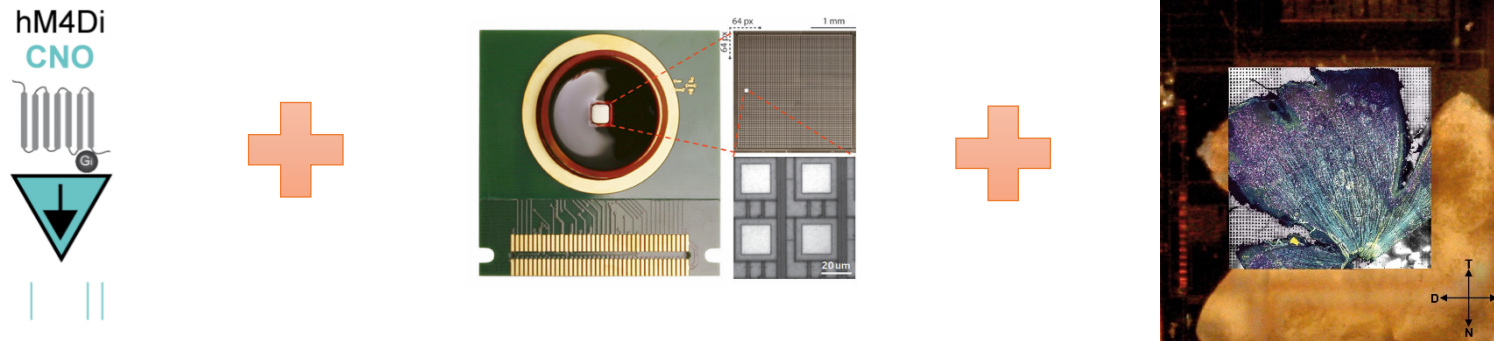
- Identify RGCs sharing a common gene expression by combining *pharmacogenetics*, large-scale high-density *electrophysiology* and *immunohistochemistry*



- 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

Aims

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



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

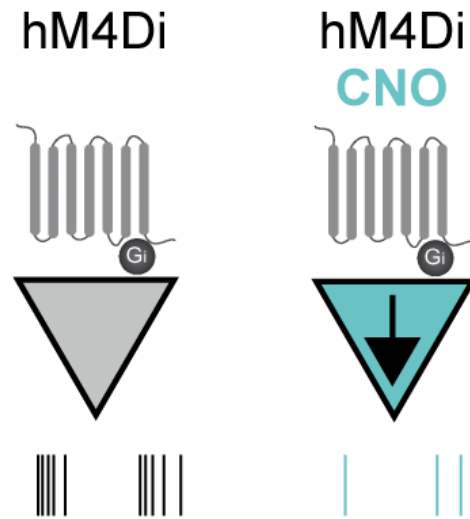
- Unravel how RGCs in these subgroups respond and interact to basic and complex visual scenes

Modelling

Numerical simulations

Pharmacogenetics - DREADD technology

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

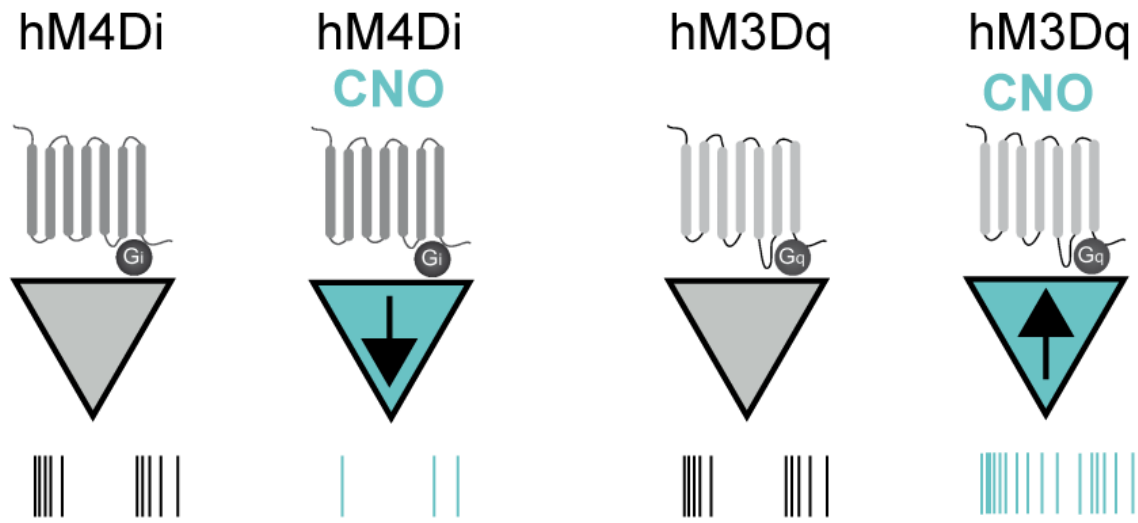


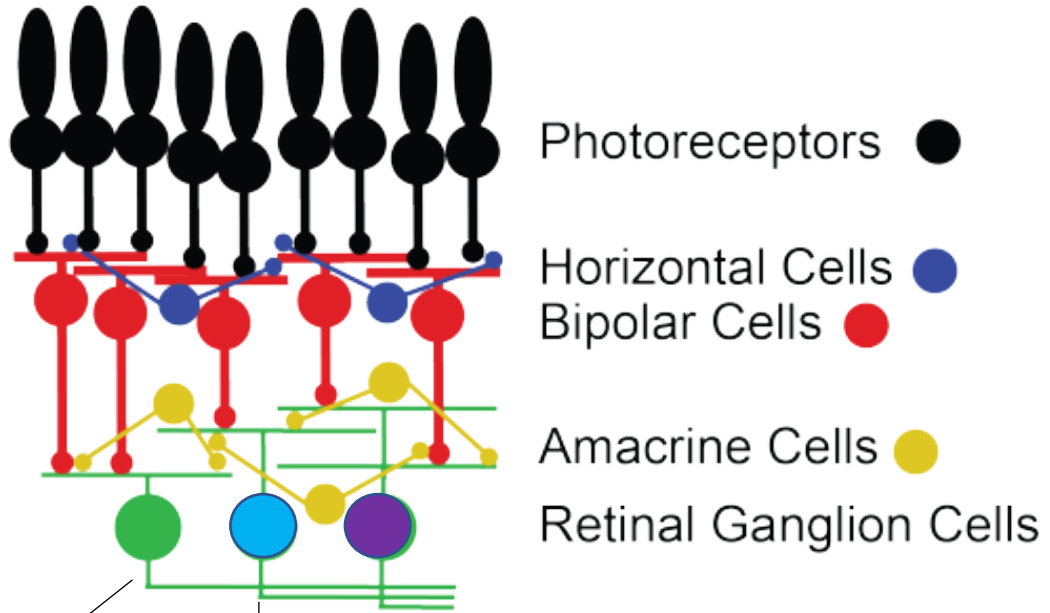
inhibitory DREADD

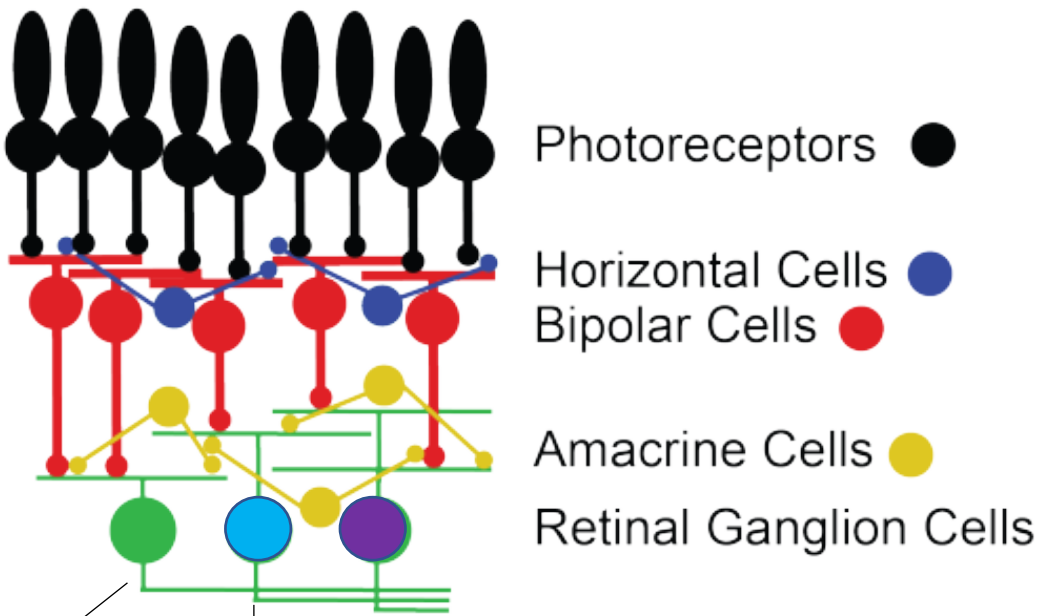


Pharmacogenetics - DREADD technology

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







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



Macular

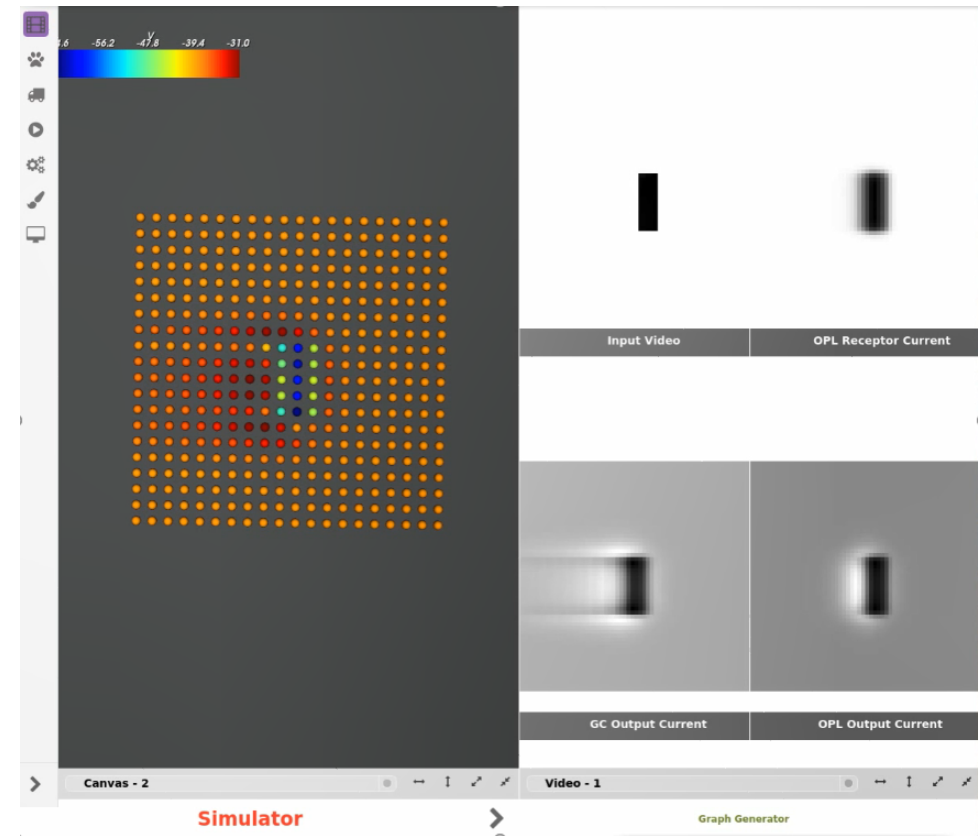


Image motion

```
graph TD; A[Image motion] --> B[Global motion]; A --> C[Differential 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

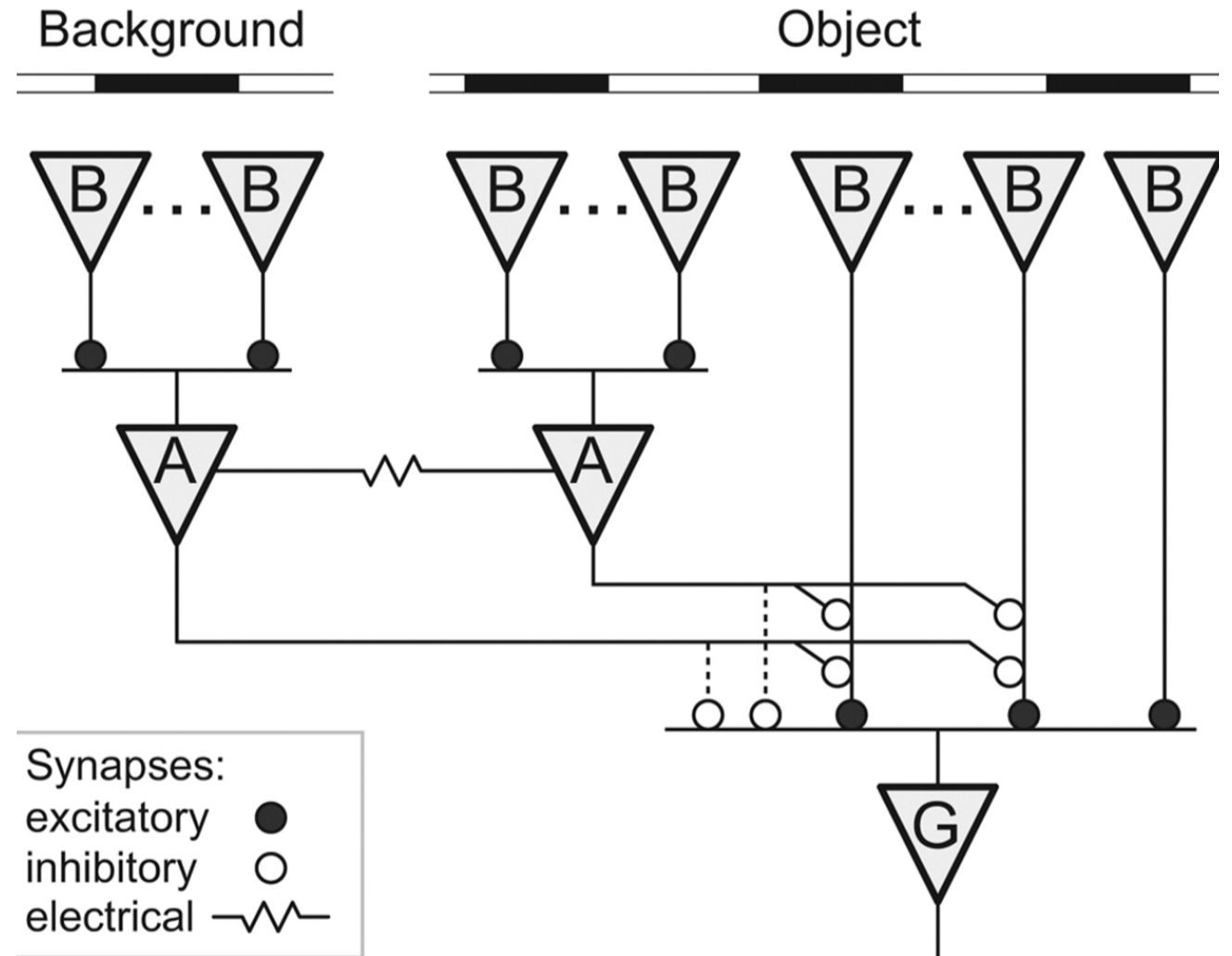


Background & Object moving

Retinal circuit related to motion

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

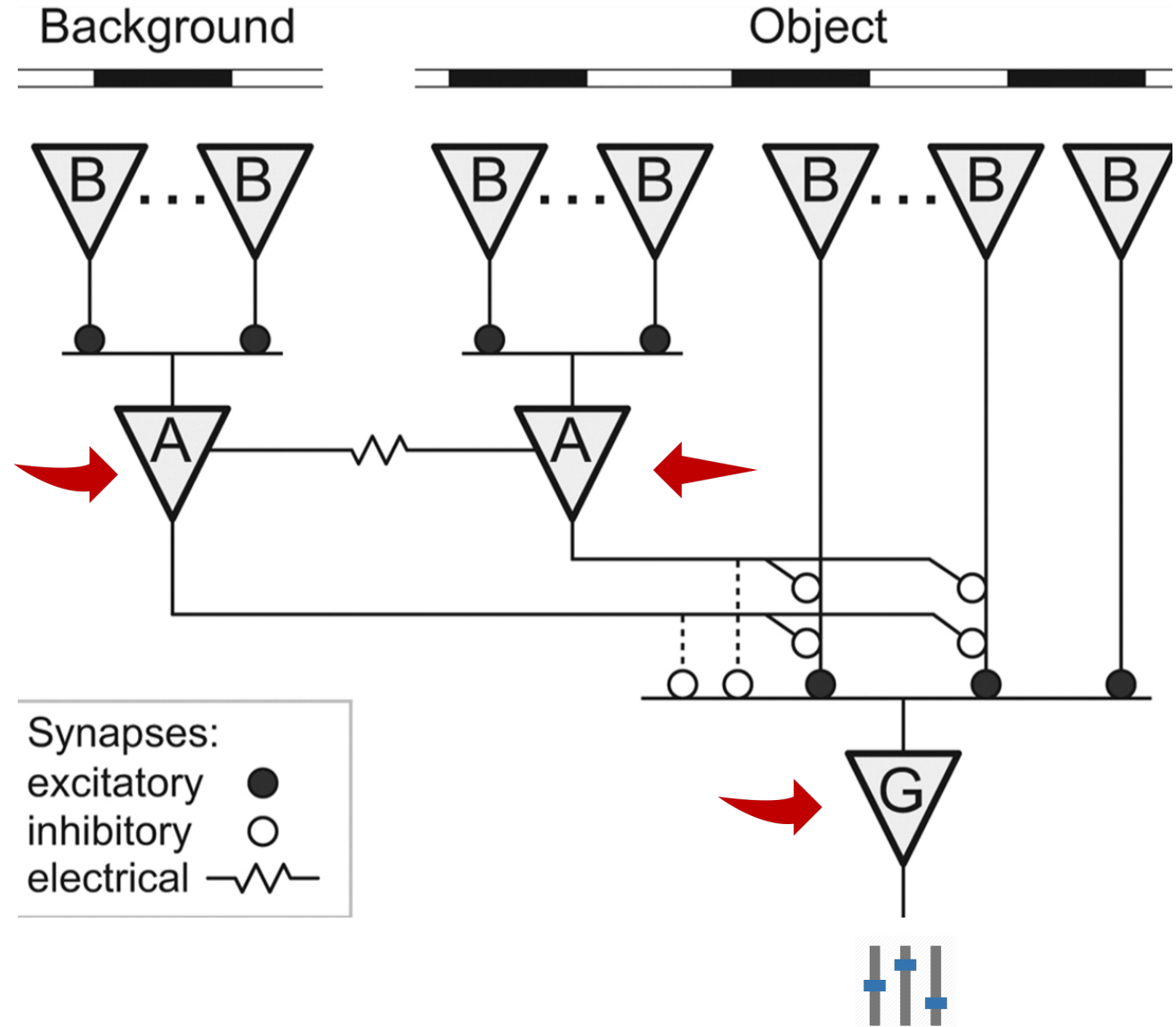
Background region: Inhibitory input to the ganglion cell (G) from amacrine cells (A).



CNO effect on the circuit

DREADDs on :

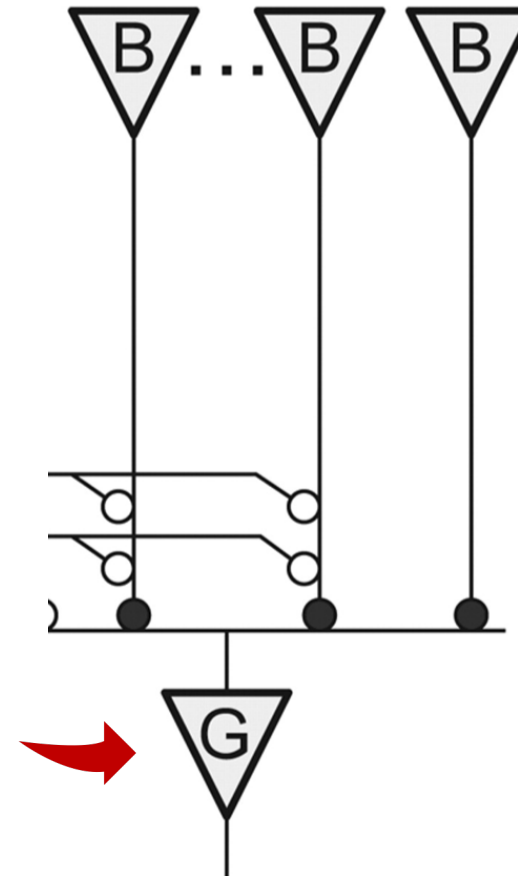
- Amacrine cells (ACs) and/or
- Ganglion cells (RGCs)



CNO effect on the circuit

DREADDs on Ganglion cells (RGCs)

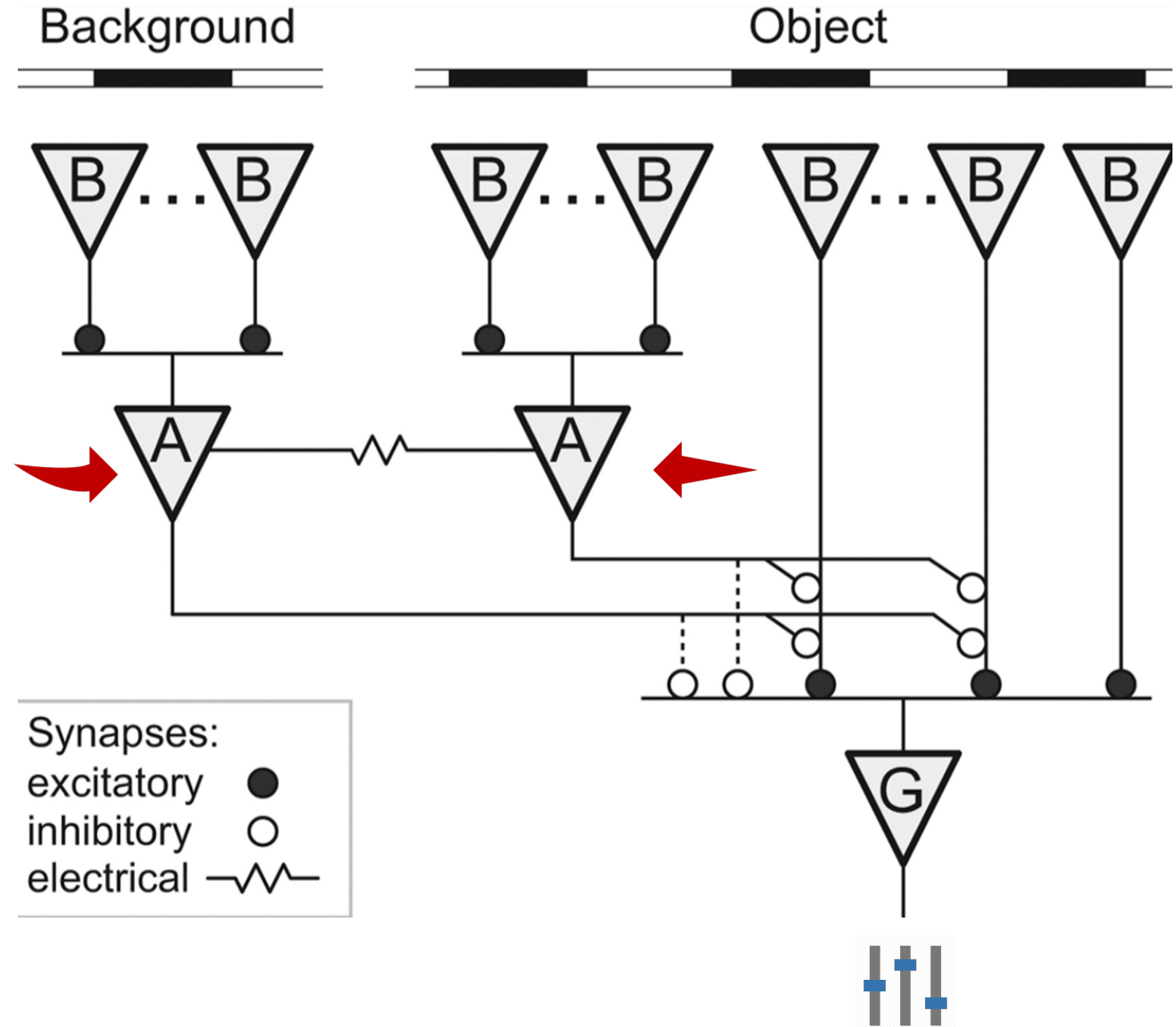
- If excitatory, the neuronal activity will increase
- If inhibitory, the neuronal activity will decrease



CNO effect on the circuit

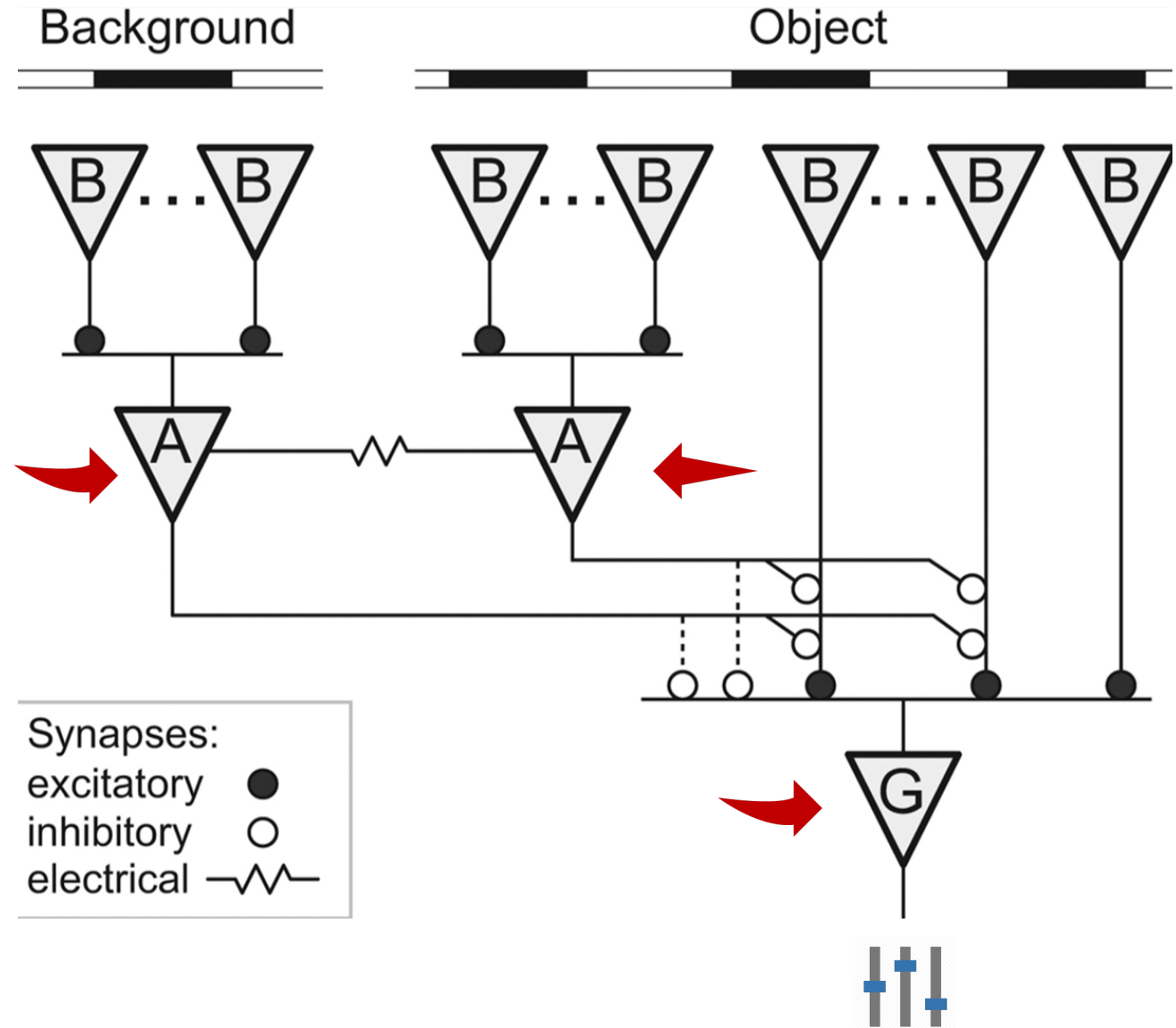
DREADDs on Amacrine cells (ACs):

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

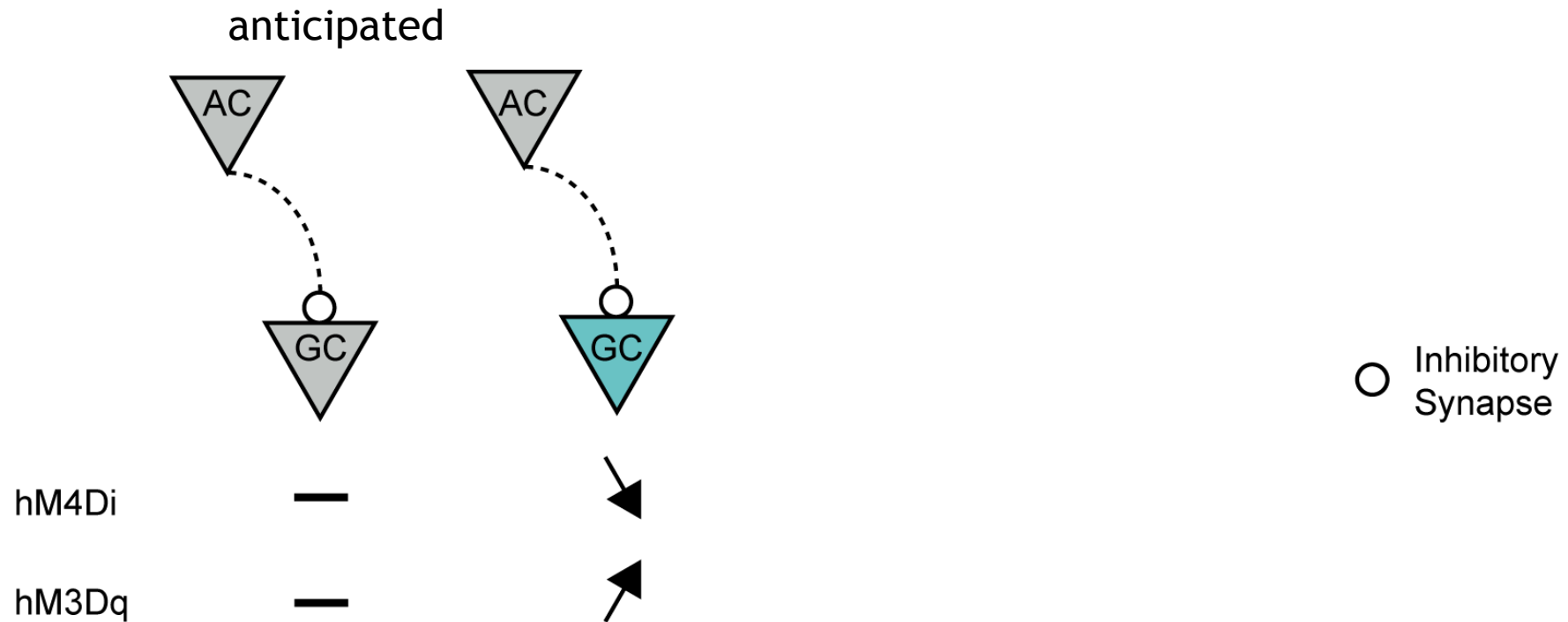


CNO effect on the circuit

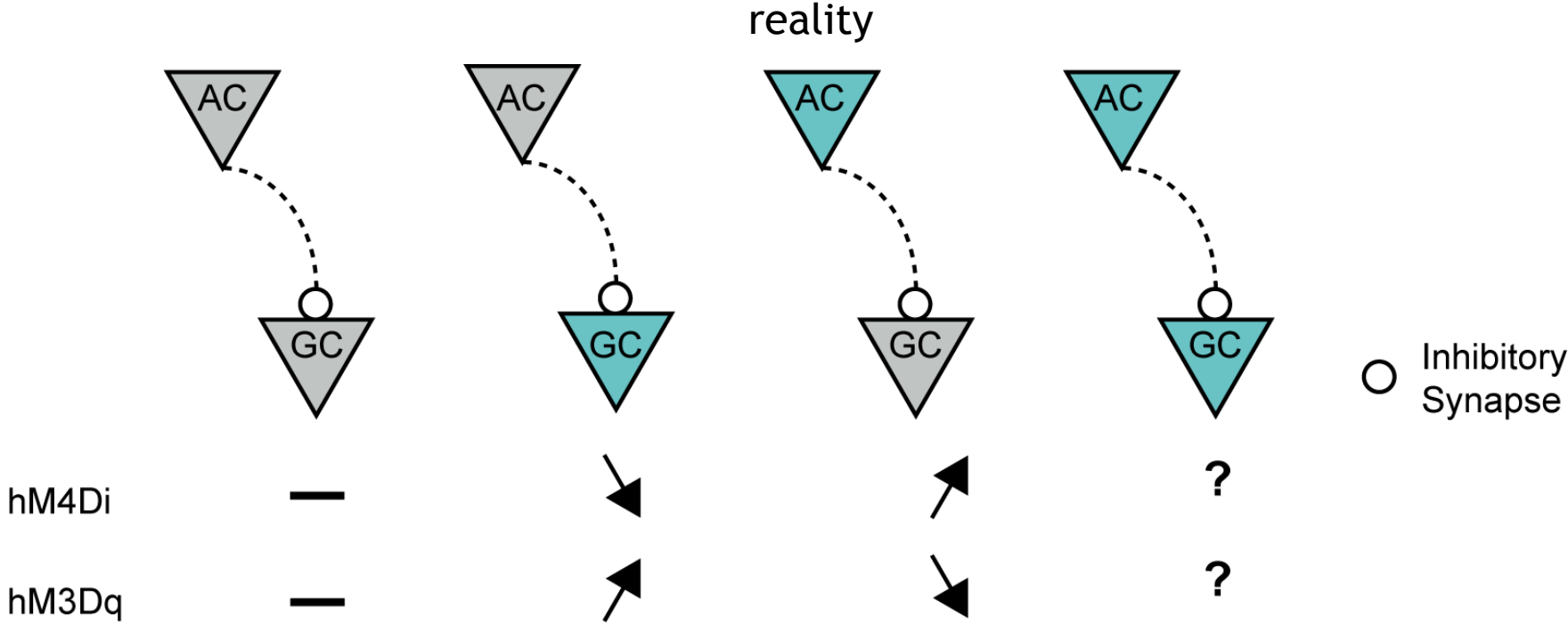
DREADDs on : ACs AND RGCs



Electrophysiological characterisation of Scnn1a and Grik4 DREADD RGCs

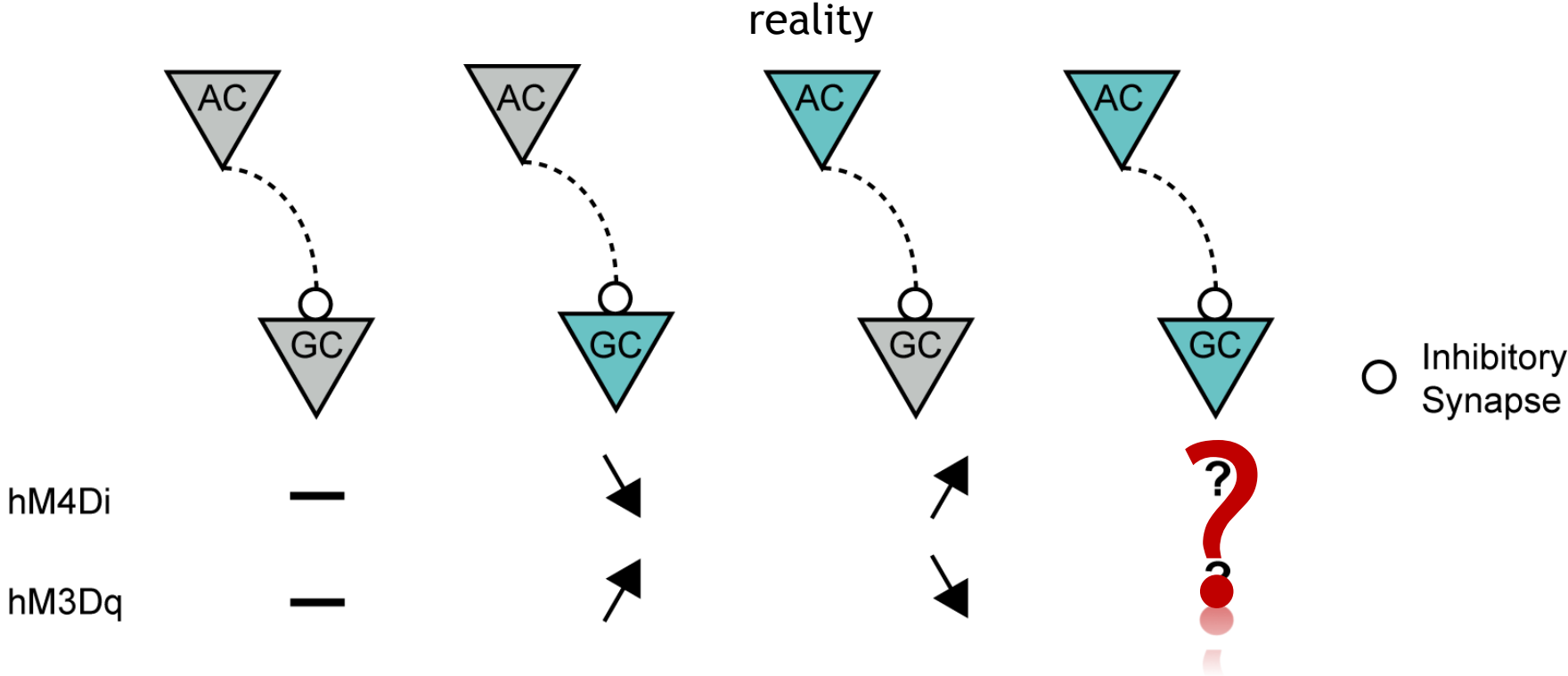


Electrophysiological characterisation of Scnn1a and Grik4 DREADD RGCs



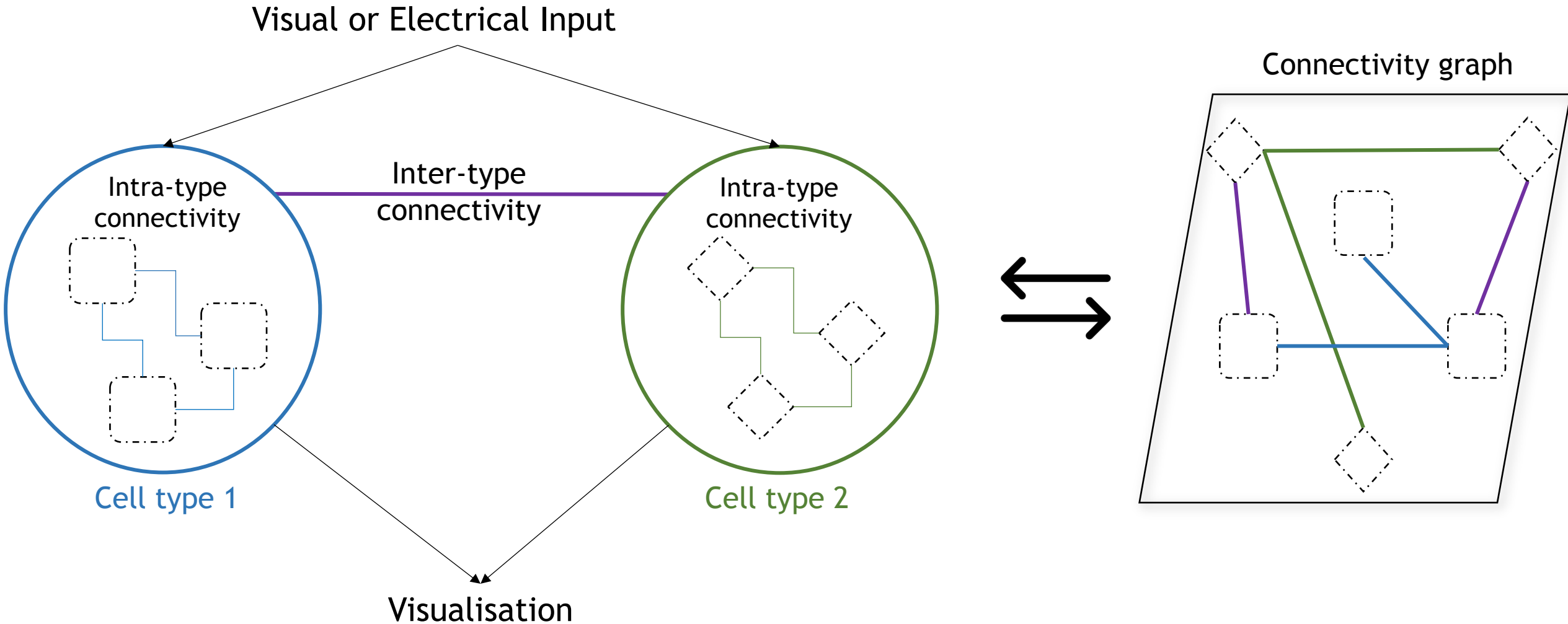
DREADDs in ACs makes the interpretation of functional results from DREADD-expressing RGCs more challenging.

Electrophysiological characterisation of Scnn1a and Grik4 DREADD RGCs

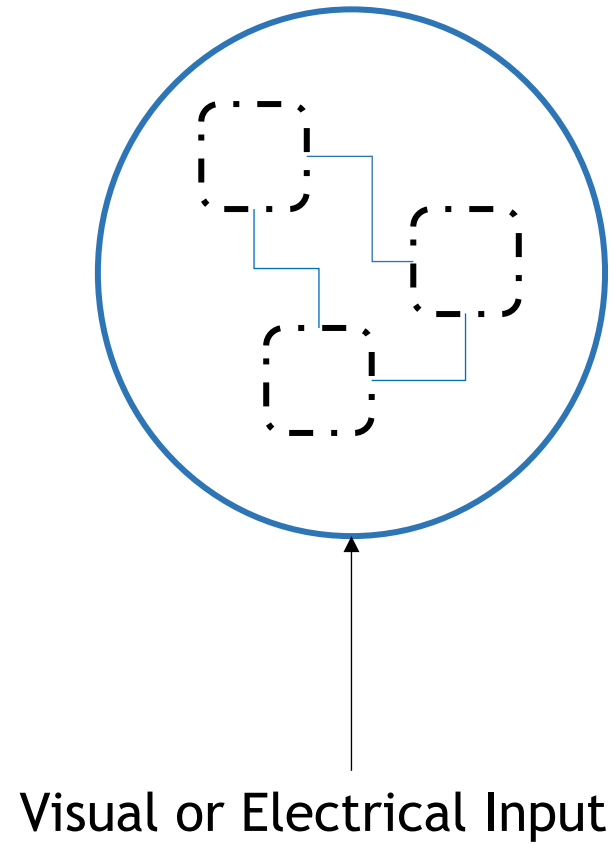


Solution: Study it numerically

General structure

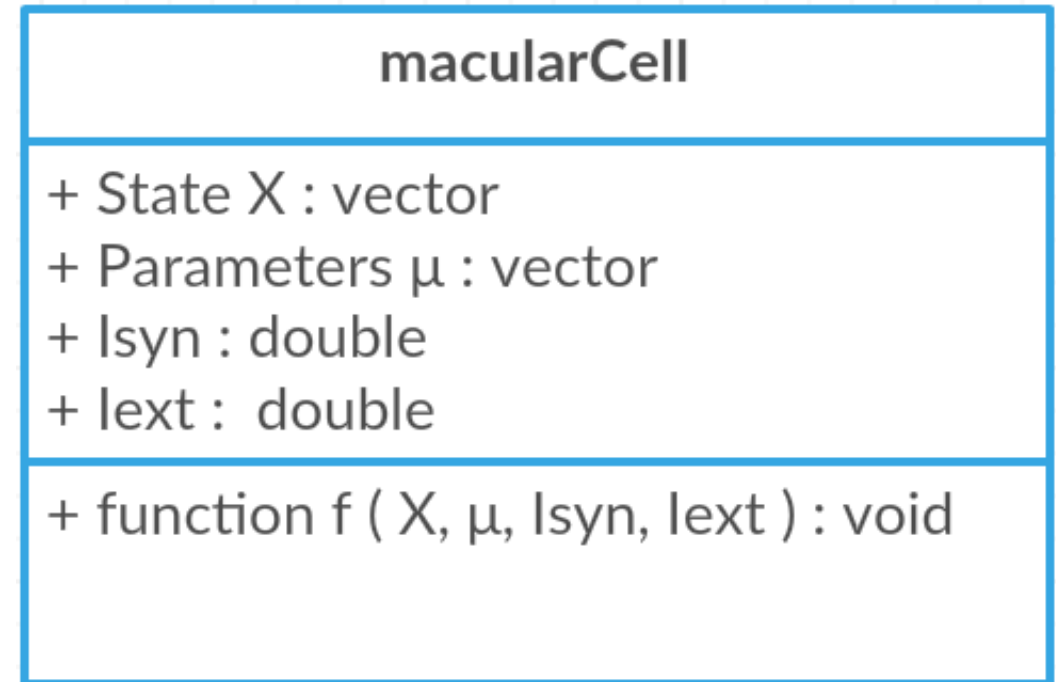


Basic building blocks - cell



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

macularCell
+ State X : vector
+ Parameters μ : vector
+ I_{syn} : double
+ I_{ext} : double
+ function $f (X, \mu, I_{syn}, I_{ext}) : void$

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
- ✓ A function controlling the cell's evolution with a differential equation

macularCell
+ State X : vector
+ Parameters μ : vector
+ I_{syn} : double
+ I_{ext} : double
+ function $f (X, \mu, I_{syn}, I_{ext}) : void$

Cell

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

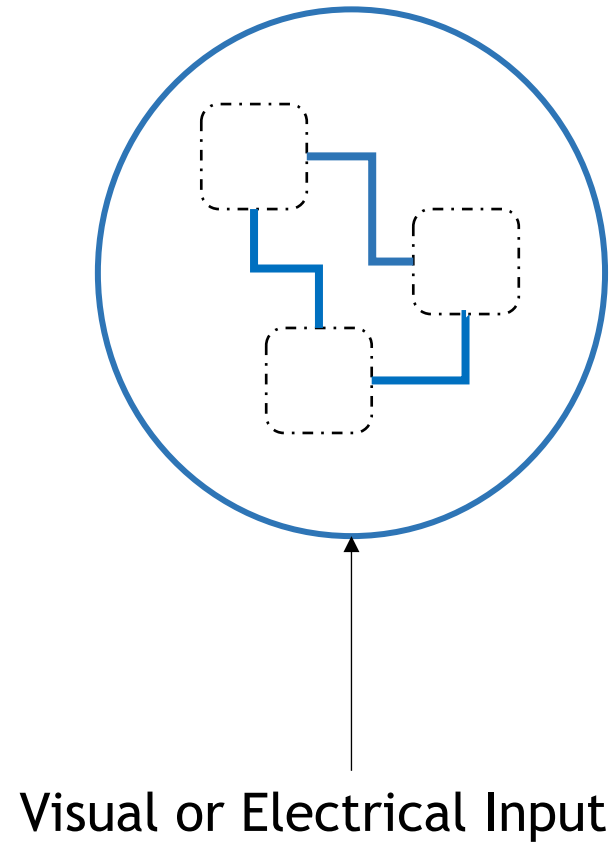
macularCell
+ State X : vector + Parameters μ : vector + Isyn : double + Iext : double
+ function $f (X, \mu, Isyn, Iext) : void$

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
- ✓ 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

macularCell
+ State X : vector
+ Parameters μ : vector
+ Isyn : double
+ Iext : double
+ function $f (X, \mu, Isyn, Iext) : void$

Basic building blocks - synapse



Synapse

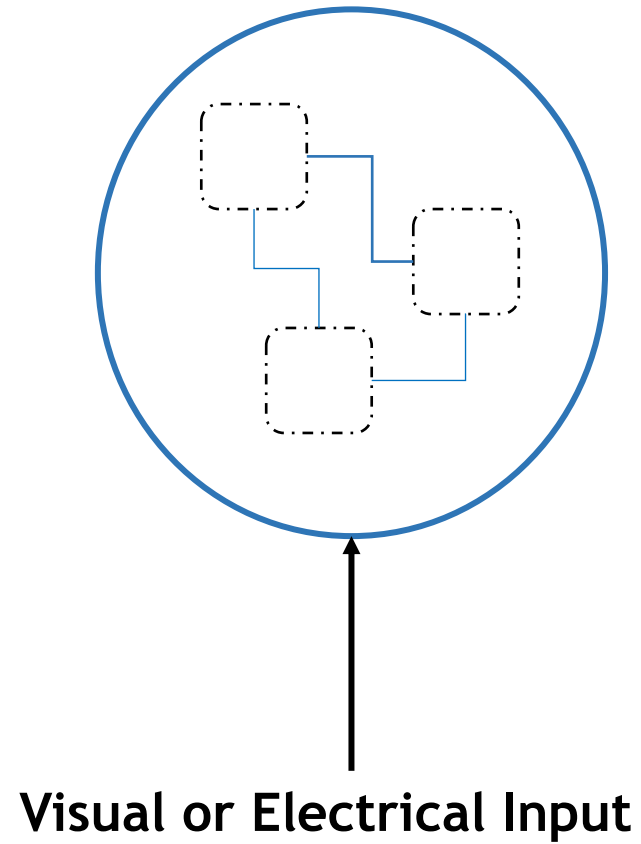
macularSynapse

+ Variables X : vector
+ Parameters μ : vector

+ computeSynapticCurrent (X , μ , pre, post) : void

- ✓ 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



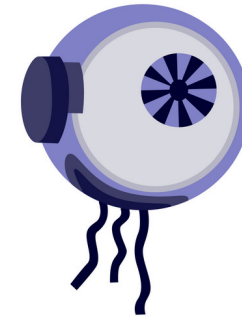
Visual Input



Virtual Retina module

- ✓ Emulate the outer plexiform layer (OPL) current

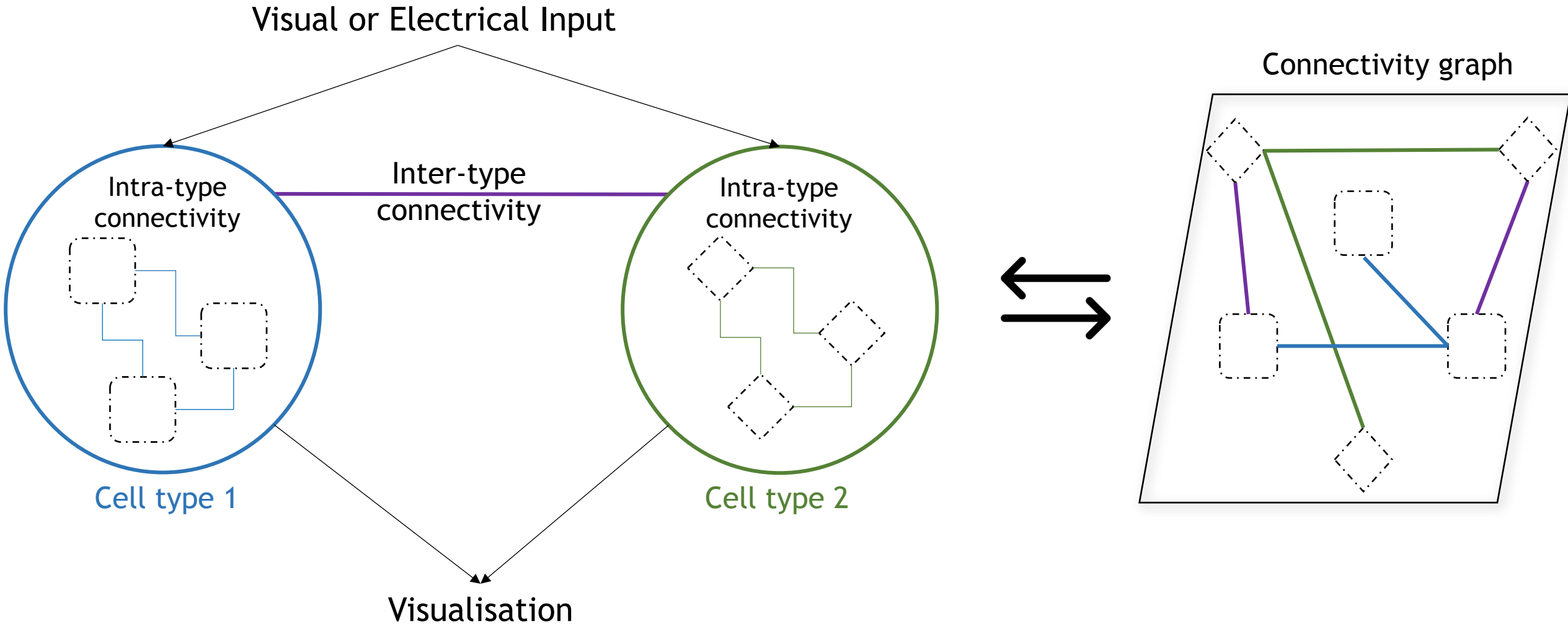
A.Wohrer et al., 2009



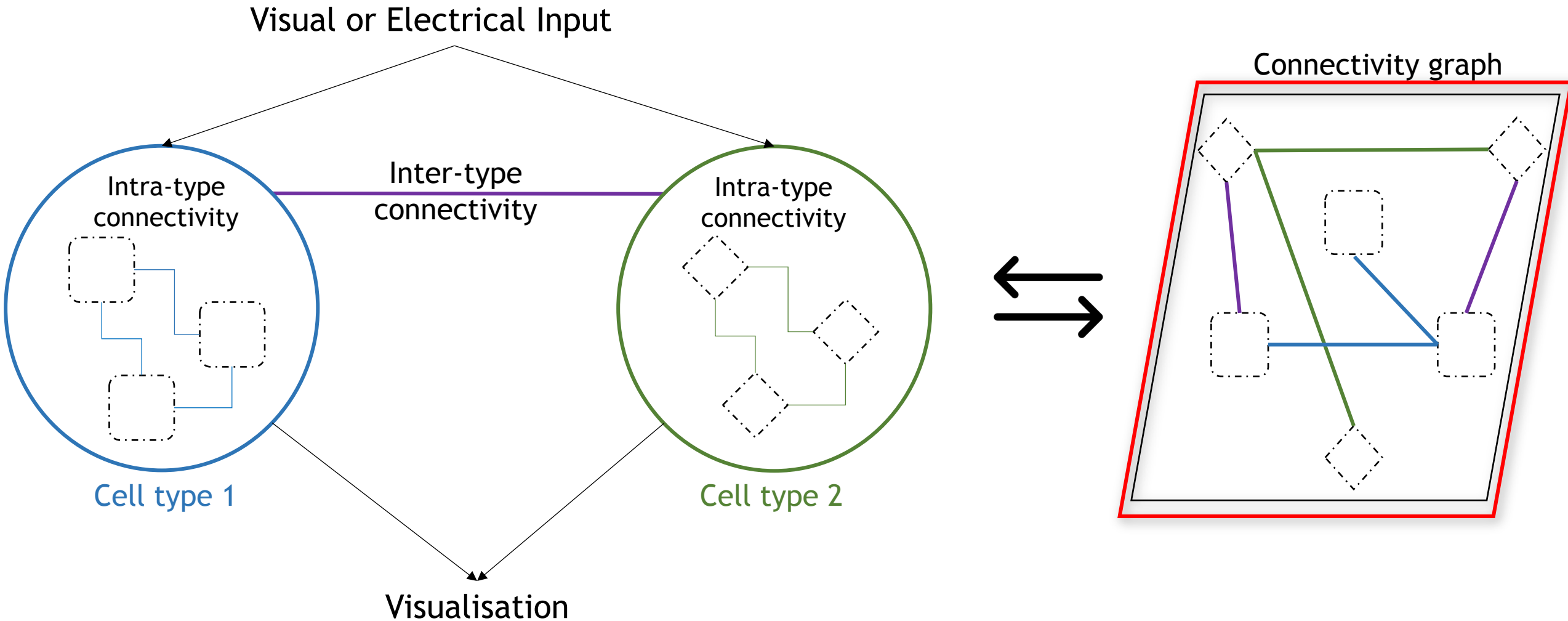
Retinal prosthesis

- ✓ Emulate the electric current provided by an electrode

General structure



General structure



Graph

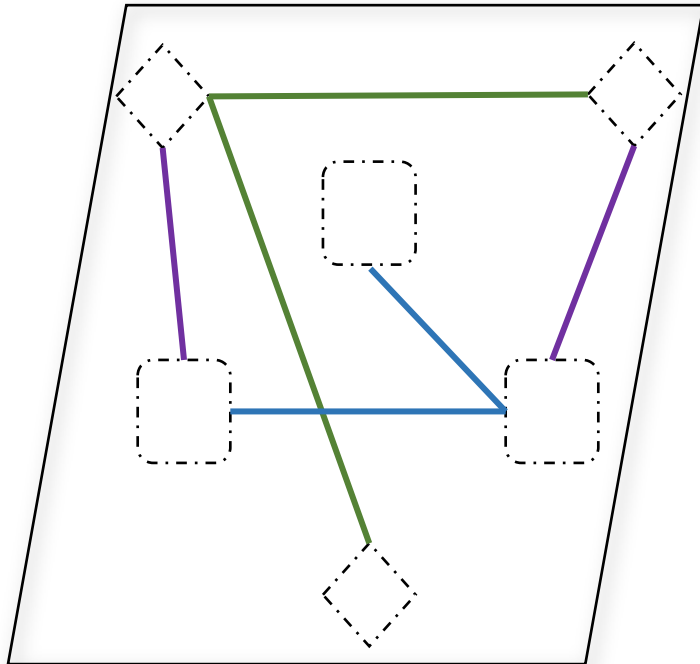
macularGraph

+ cells : macularCell
+ synapses : macularSynapse
+ CellCoordinates: vector
+ SynapseIndices: vector

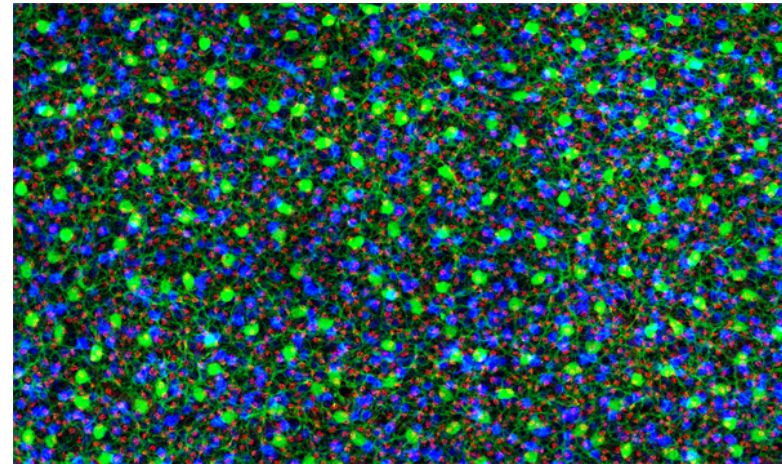
- ✓ Cell types
- ✓ Synapse types
- ✓ Cell coordinates
- ✓ Synapse indices

Graph

Connectivity graph



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



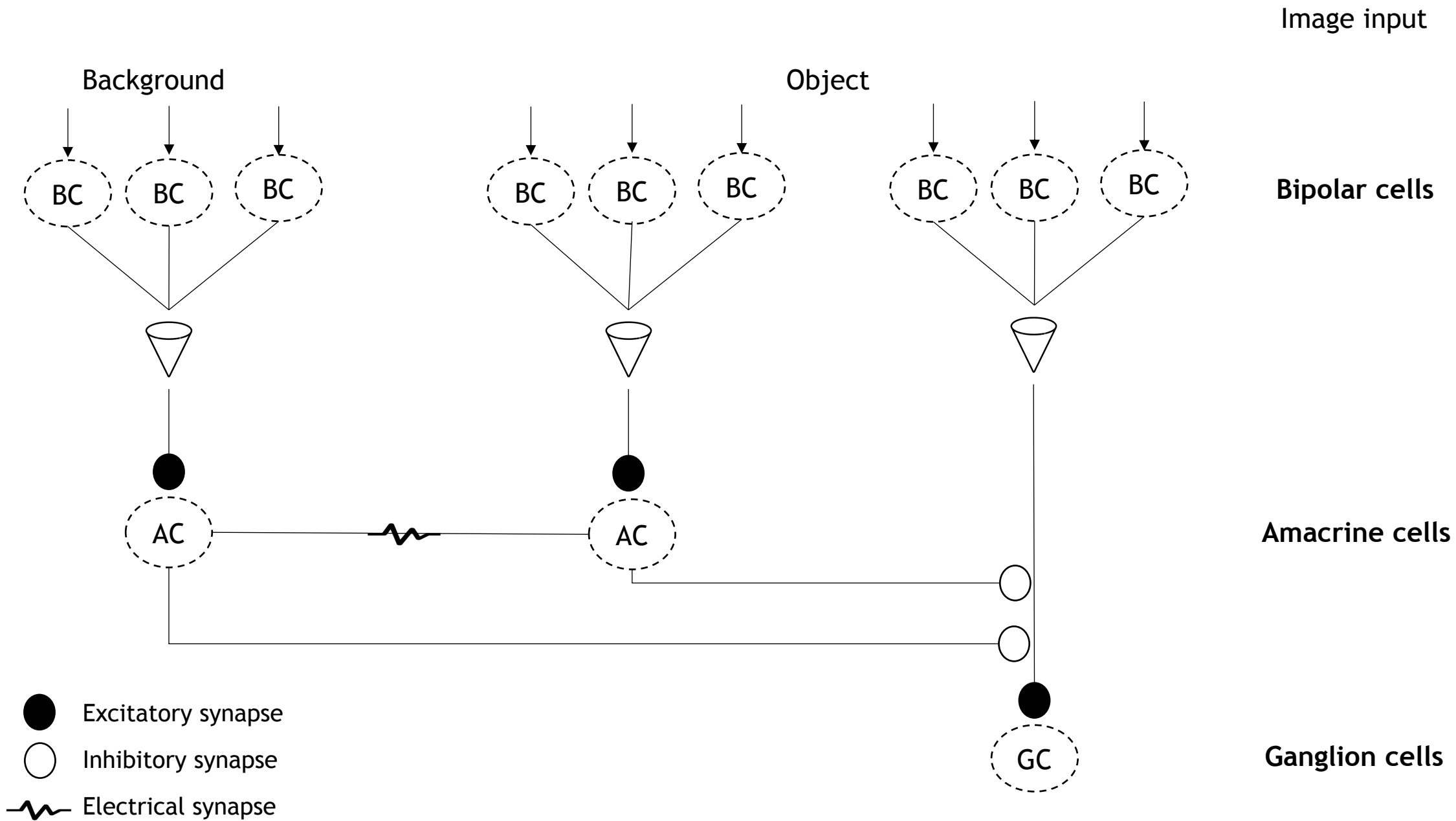


Image input

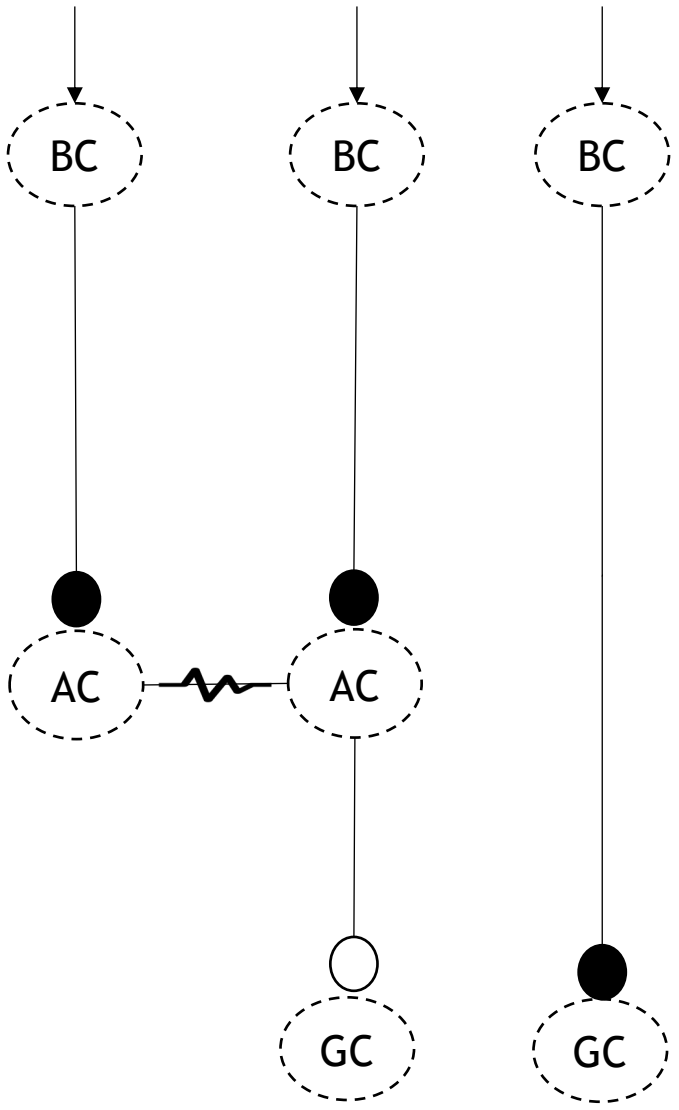
Background

Object

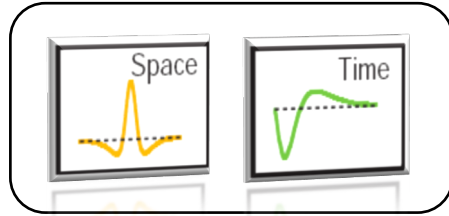
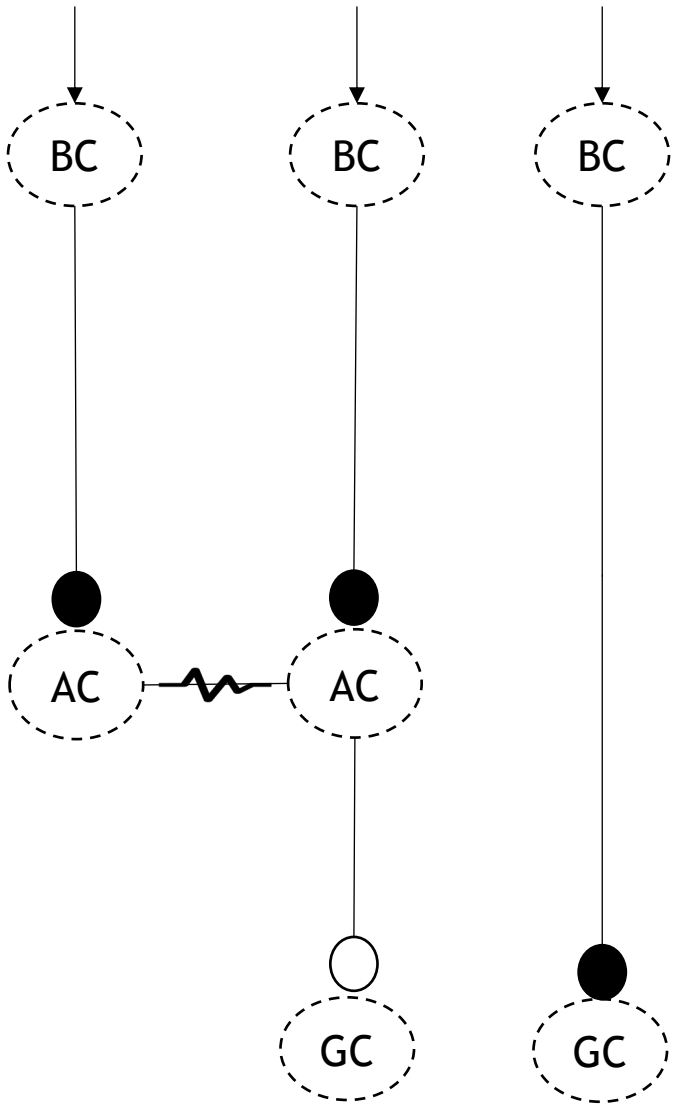
Bipolar cells

Amacrine cells

Ganglion cells

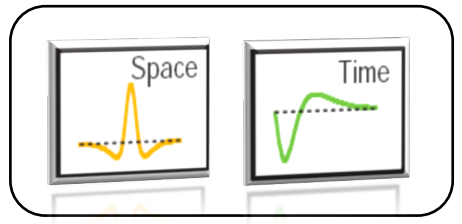
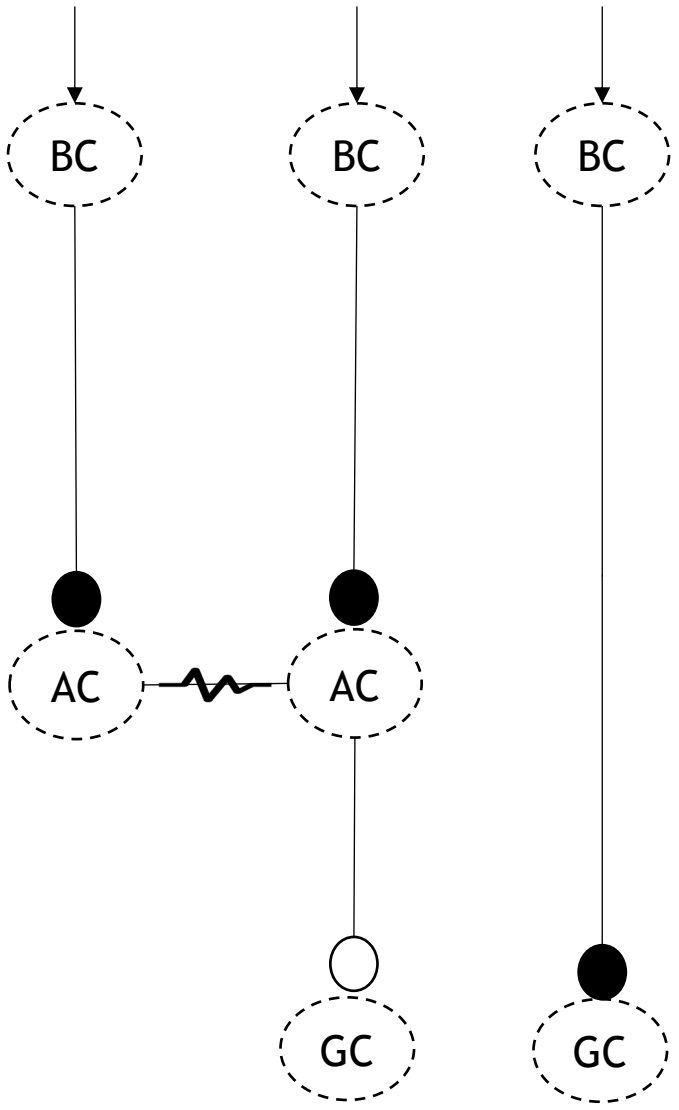


● ○ Chemical synapse
— Electrical synapse



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

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



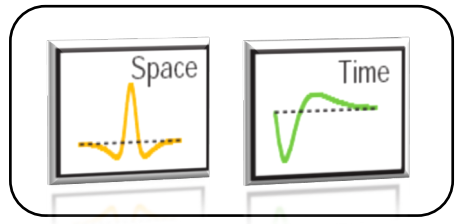
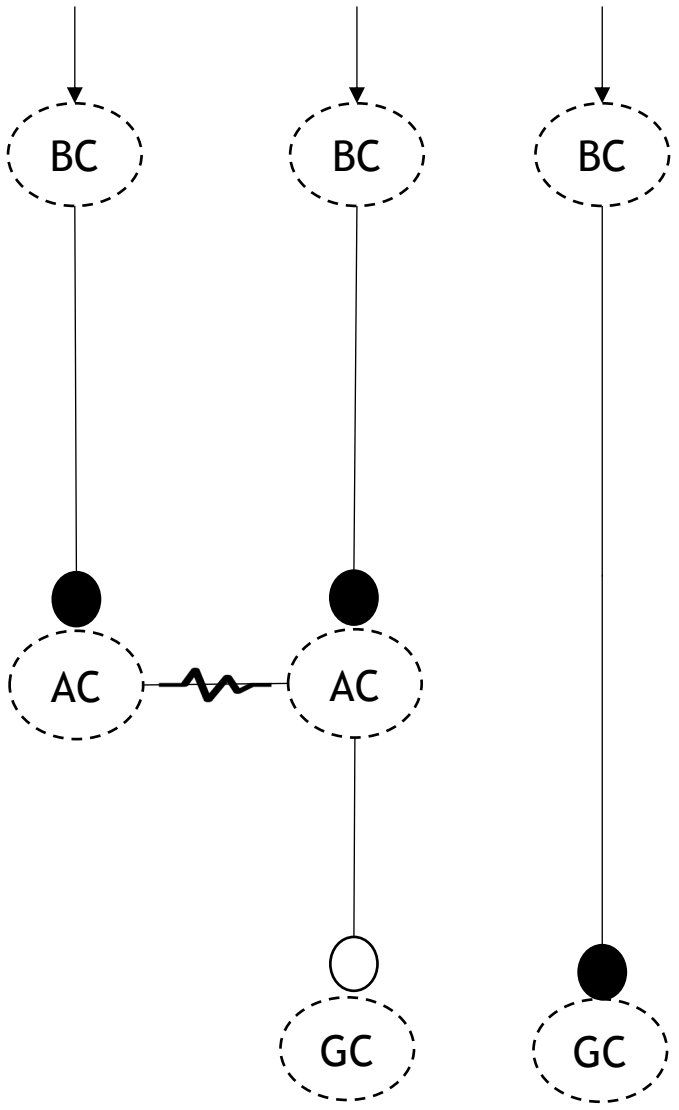
● ○ Chemical synapse
 ~~~~~ Electrical synapse

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

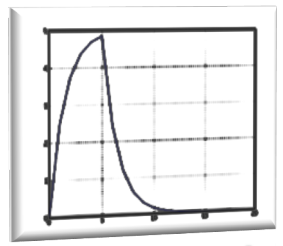
$$\int (S * K)(x, y, t)$$

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

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



Chemical synapse  
 Electrical synapse



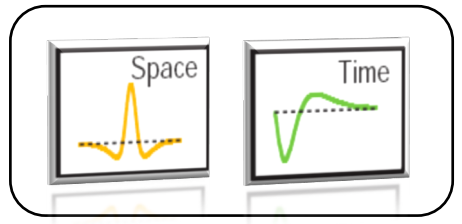
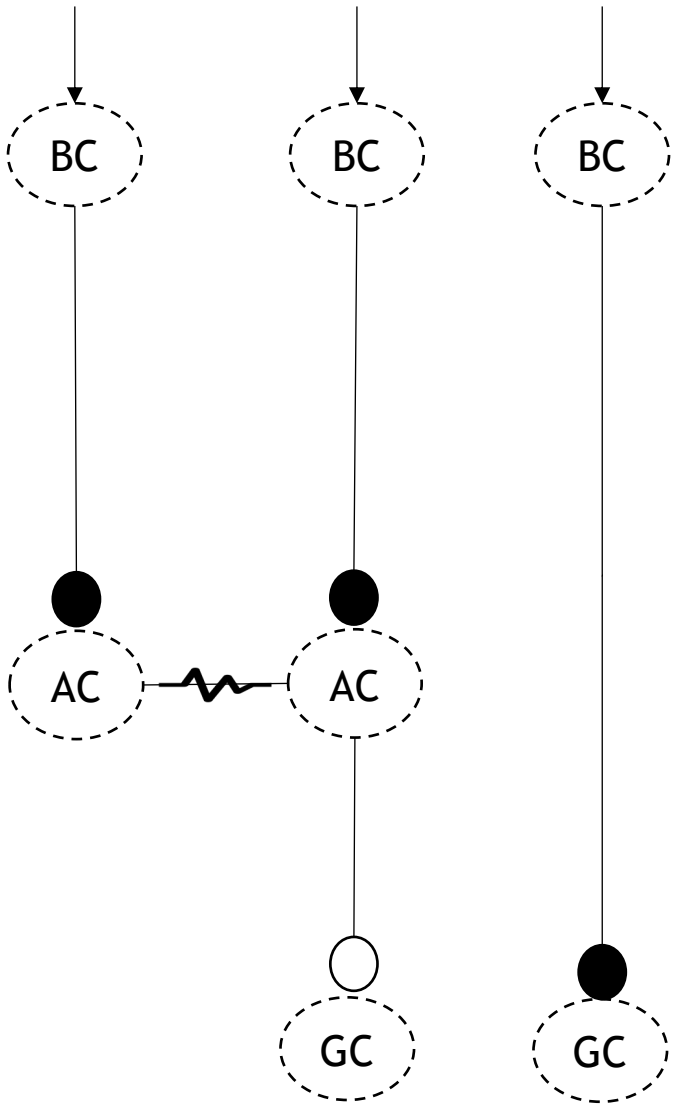
$$K(x, y, t) = K_S(x, y)K_T(t)$$

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

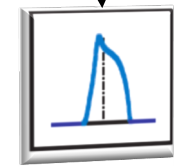
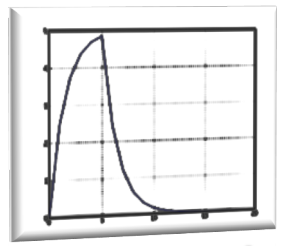
$$I_{syn} = -g_{syn} (V_{post} - E_{syn})$$

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

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



● ○ Chemical synapse  
 ~~~~~ Electrical synapse



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



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

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

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

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


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

 **All Items**
 Identifier Acetylcholine
 Settings
 Extend

Macular repository macular

Model functions

`gAch(A, gA, gammaA)`
`doc Actylcholine conductance for nicotinic receptors`
`format SymPy`

 Edition `gA * A**2 / (gammaA + A**2)`

State


All

Acetylcholine


+ New


Cell

Synapse

 File


Write C++ files

 Themes

 Choose Theme >

Model synaptic current

`- gAch(pre_A, post_gAchMax, post_gammaAch) * (post_V - post_VAch)`

 Cancel Save

Add parameter

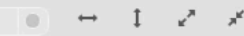
Add function

Delete function



Ganglions

Video



Simulator



Graph Generator

0.00 0.00 0.00 0.00 0.00

Canvas - 2

Simulator

| Input Video | OPL Receptor Current |
|-------------------|----------------------|
| | |
| GC Output Current | OPL Output Current |
| | |

Video - 1

All Items

Video Input

Browse Video **test_small**

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 **105000**

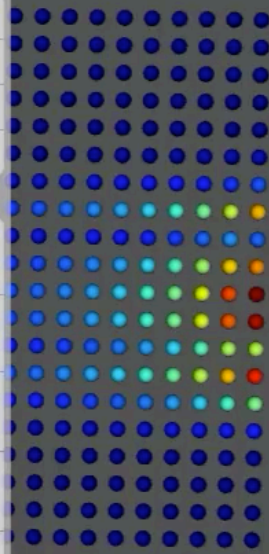
Save/Restore parameters

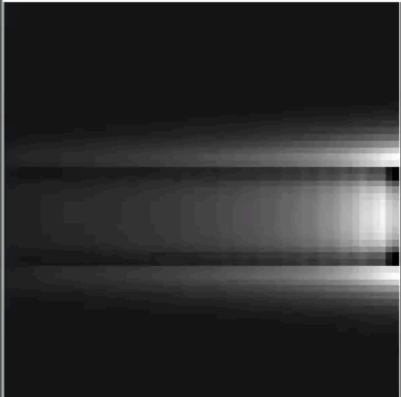
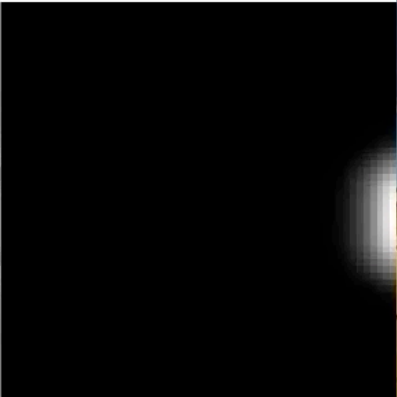


Save frequency **0**

Model **Prosthesis**

Parameters

- MorrisLecar >
- HodgkinHuxley >
- SAC >
- BipolarGainControl >
- MorrisLecarAch >



| Input Video | OPL Receptor Current |
|---|---|
|  |  |
| GC Output Current | OPL Output Current |
|  |  |

Video - 1

Simulator

The background features several microscopy images of cells expressing a green fluorescent protein. The cells are arranged in a hexagonal pattern. The largest cell in the center shows a clear nucleus and radiating cytoplasmic structures. Other cells are shown in various orientations, some with more diffuse fluorescence. A dark grey rectangular box with a blue tab is overlaid on the right side of the image.

Thank you!

Questions?