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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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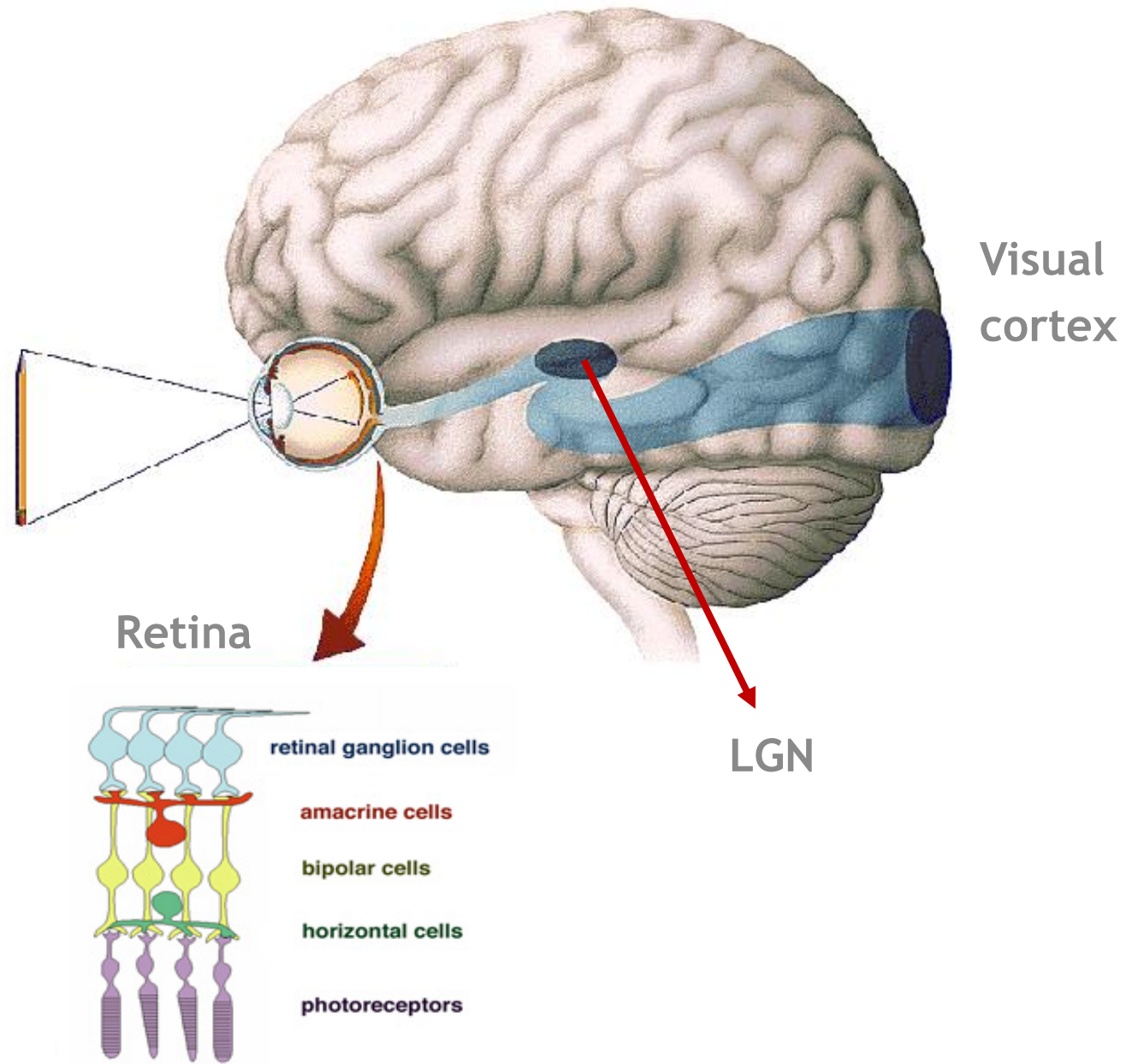
NeuroMod Institute meeting

Probing retinal function with a multi-layered simulator

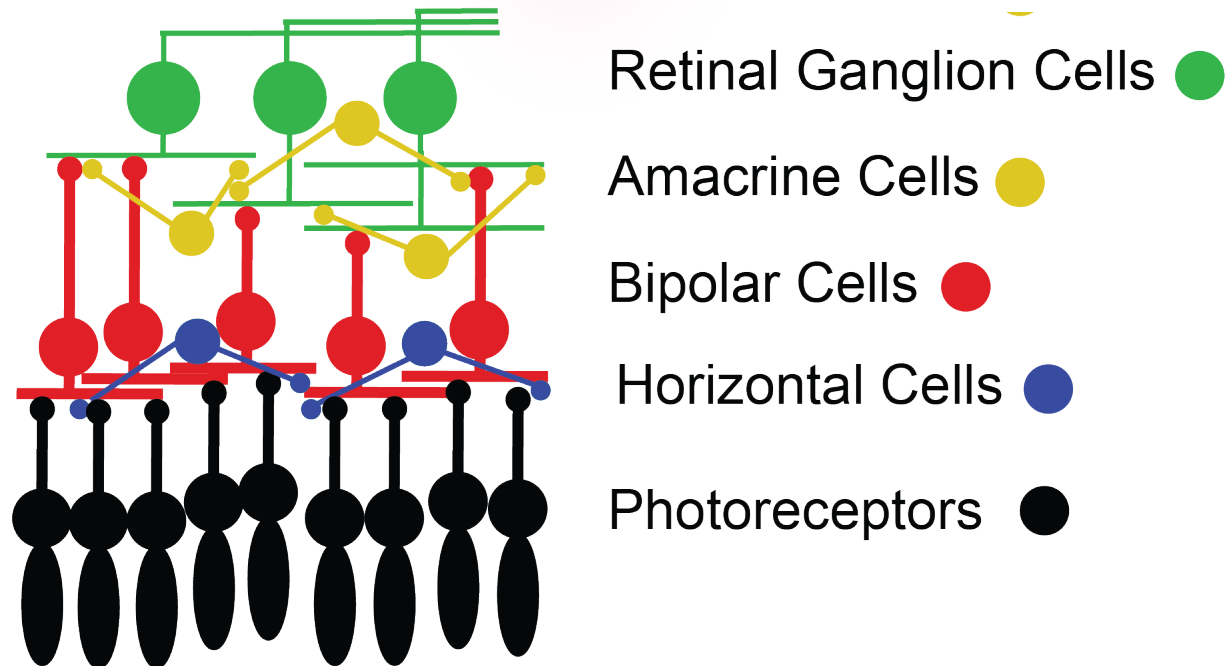
Evgenia Kartsaki^{1,2}, Bruno Cessac¹, Gerrit Hilgen², Evelyne Sernagor²

¹Biovision team, Université Côte d'Azur, Inria, France

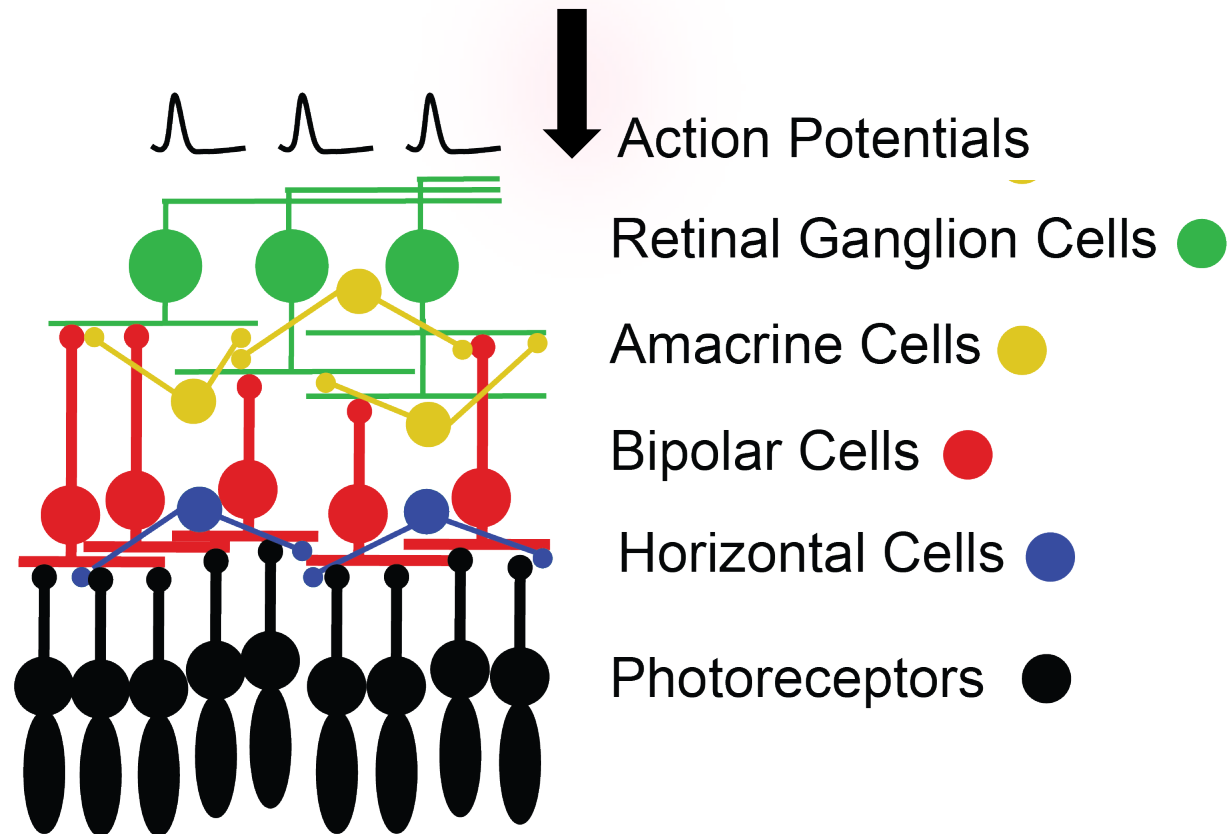
²Institute of Neuroscience, University of Newcastle, UK



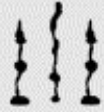
Retinal visual flow



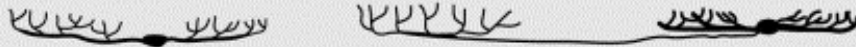
Retinal visual flow



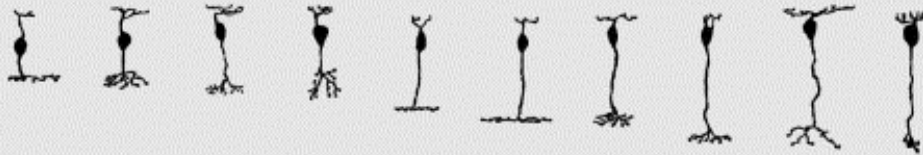
Photoreceptors



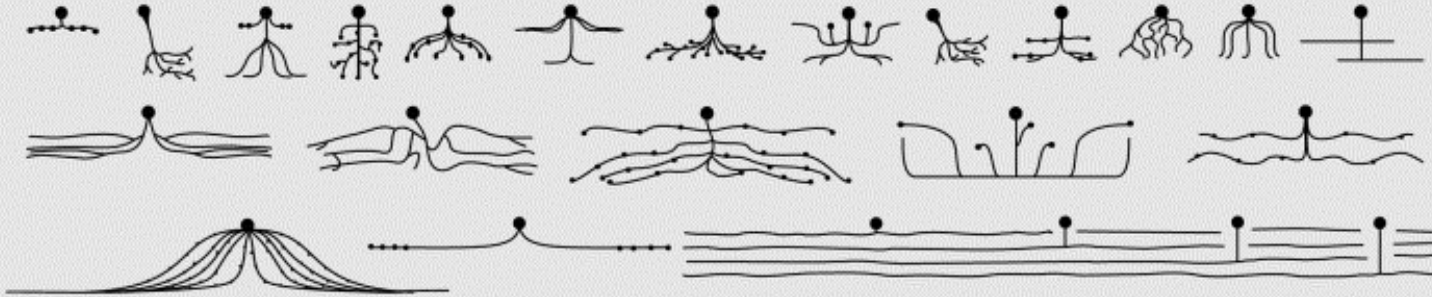
Horizontal cells



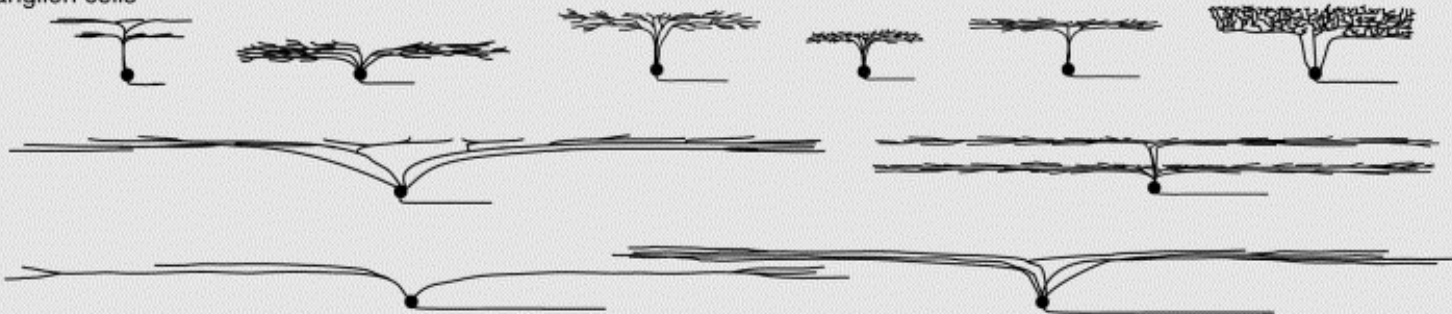
Bipolar cells



Amacrine cells



Ganglion cells



Retinal neurons inventory

Leverhulme funded project:

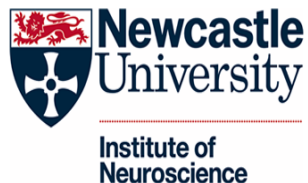
“A novel approach to functional classification of retinal ganglion cells”

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

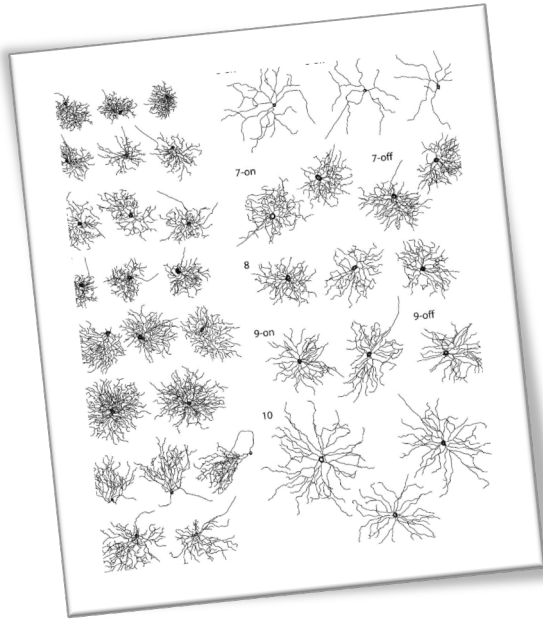
- pharmacogenetics
- large-scale retinal electrophysiology
- immunochemistry

☞ Understand their role in population encoding of complex visual scenes

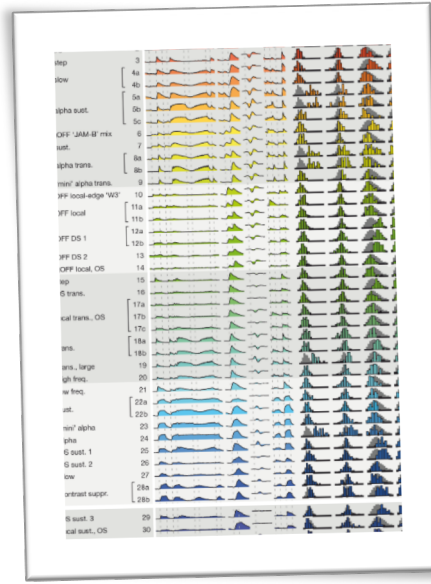
LEVERHULME
TRUST



Yet another RGC classification...



Coombs et al., 2006



Baden, Berens, Franke et al., 2016

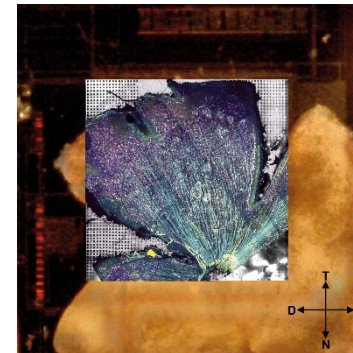
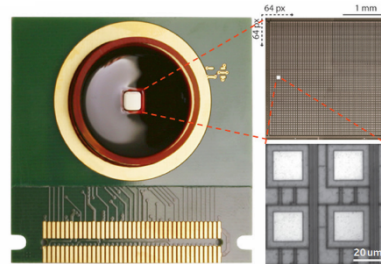
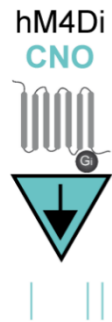


Martersteck, Hirokawa, Everts et al., 2017

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

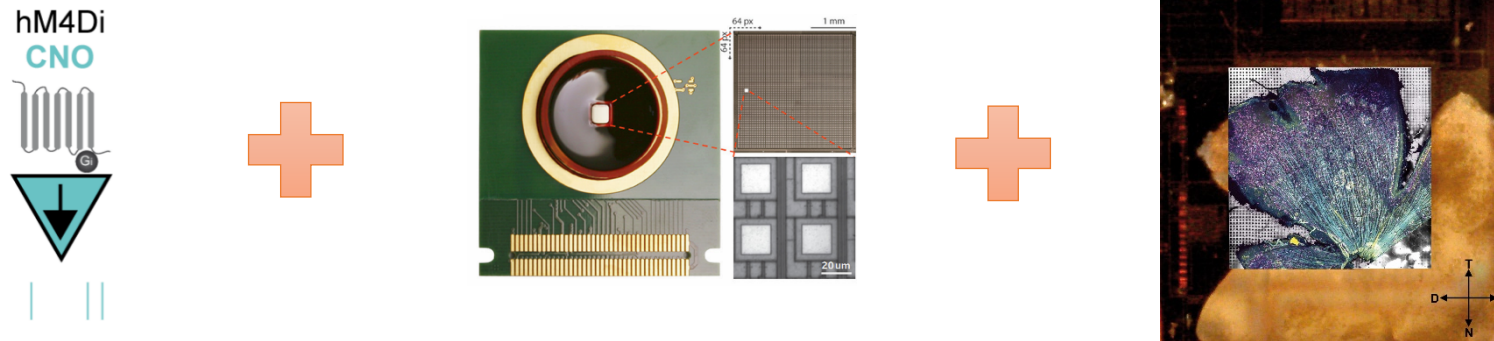
Aims

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



Aims

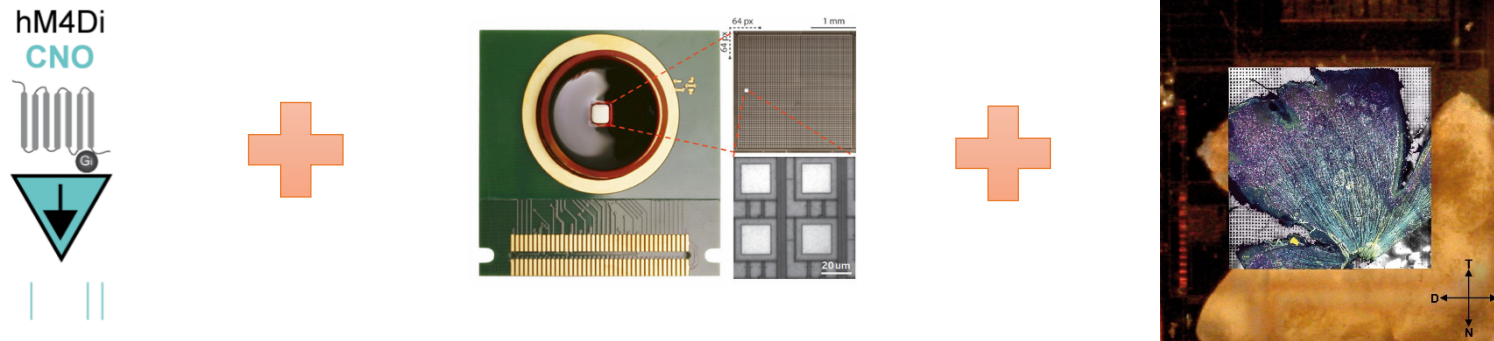
- Identify RGCs sharing a common gene expression by combining *pharmacogenetics*, large-scale high-density *electrophysiology* and *immunohistochemistry*



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

Aims

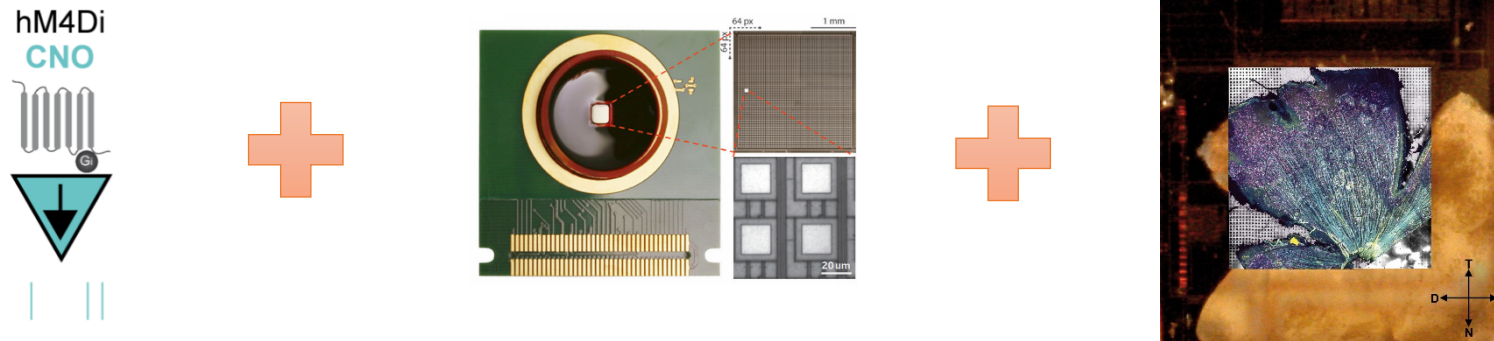
- Identify RGCs sharing a common gene expression by combining *pharmacogenetics*, large-scale high-density *electrophysiology* and *immunohistochemistry*



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- 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

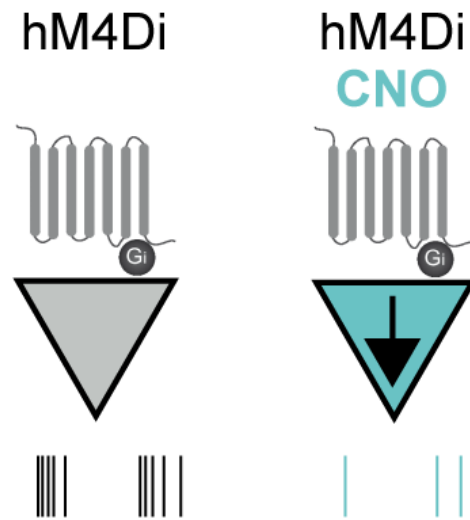
- Unravel how RGCs in these subgroups respond and interact to basic and complex visual scenes

Modelling

Numerical simulations

Pharmacogenetics - DREADD technology

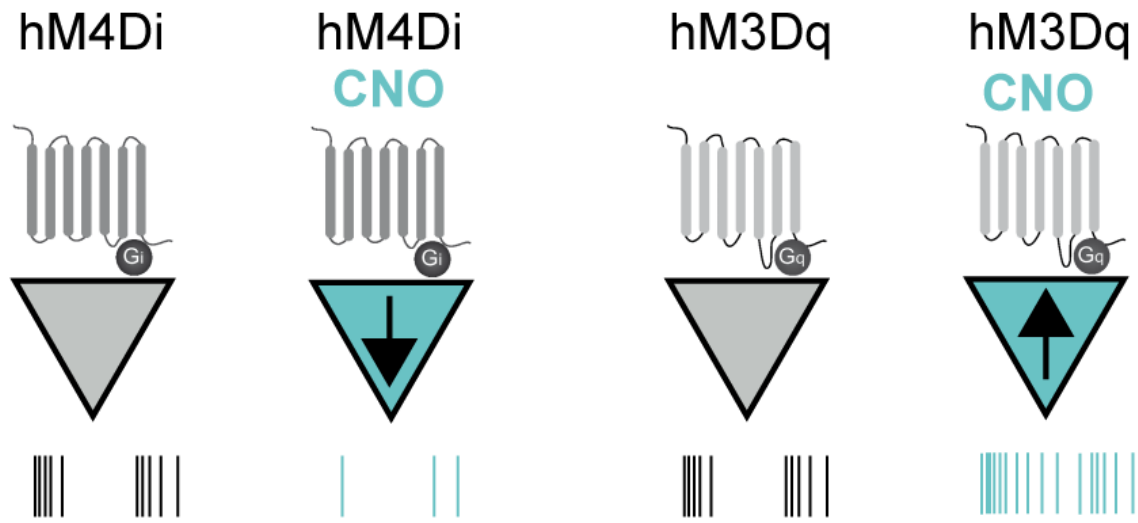
Designer **R**eceptors **E**xclusively **A**ctivated by **D**esigner **D**rugs

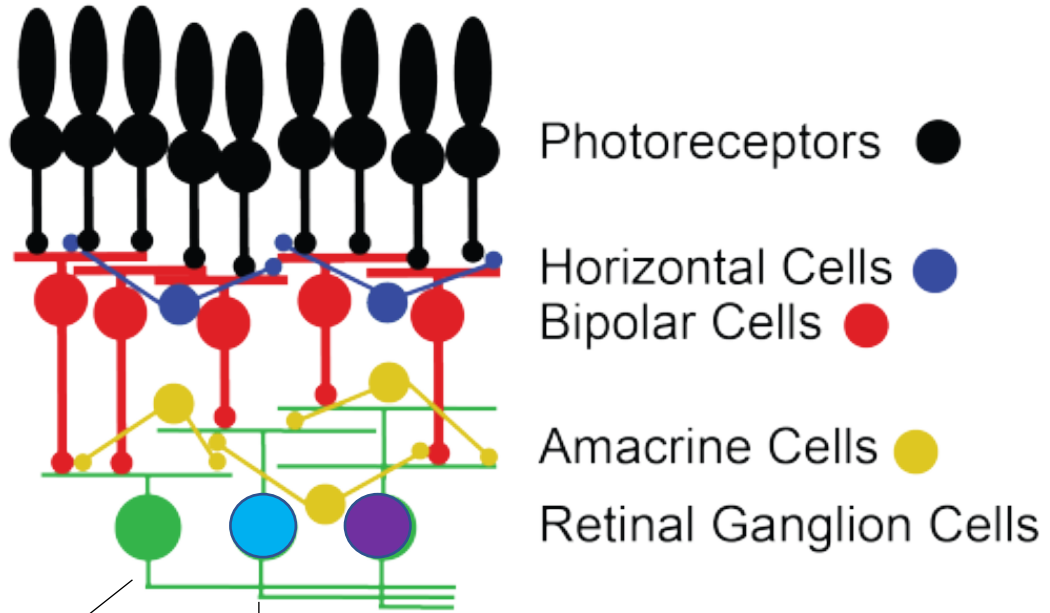


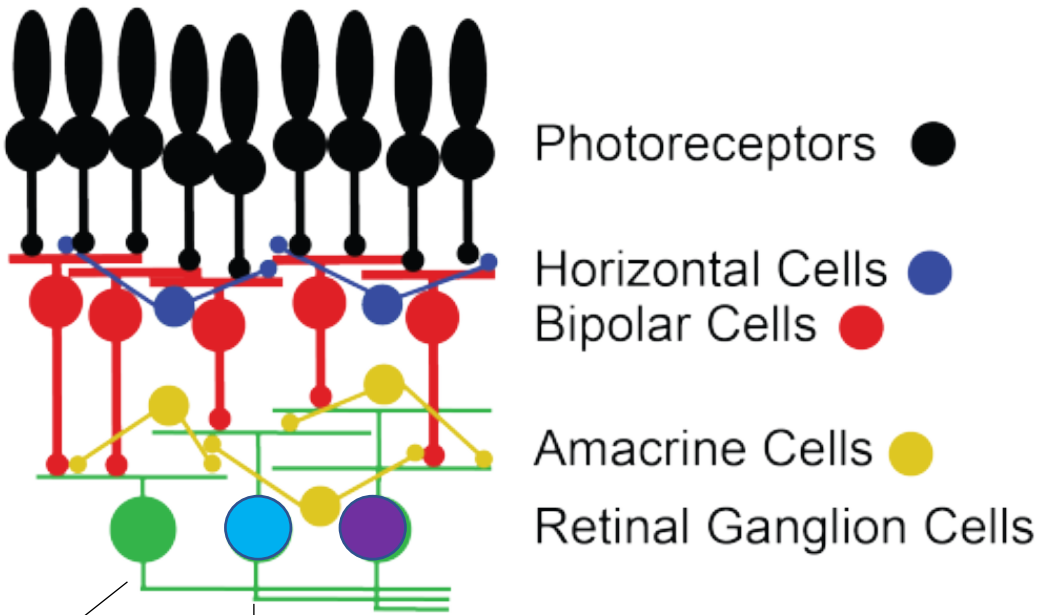
inhibitory DREADD ↘

Pharmacogenetics - DREADD technology

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







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

Macular

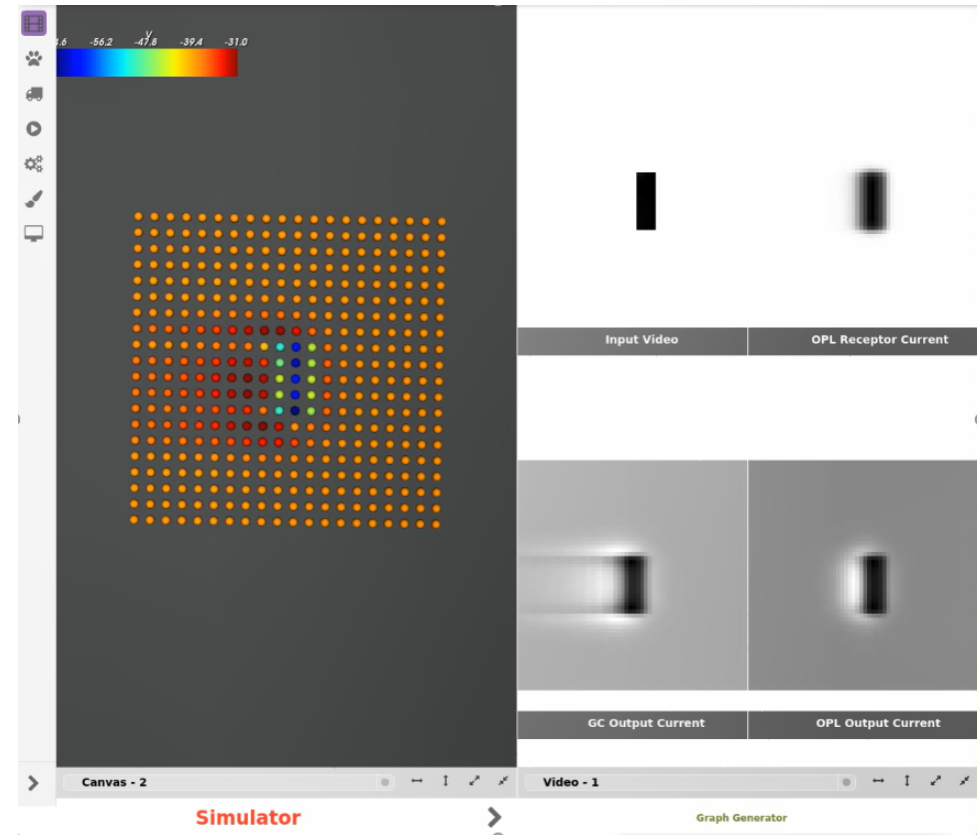


Image motion

```
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

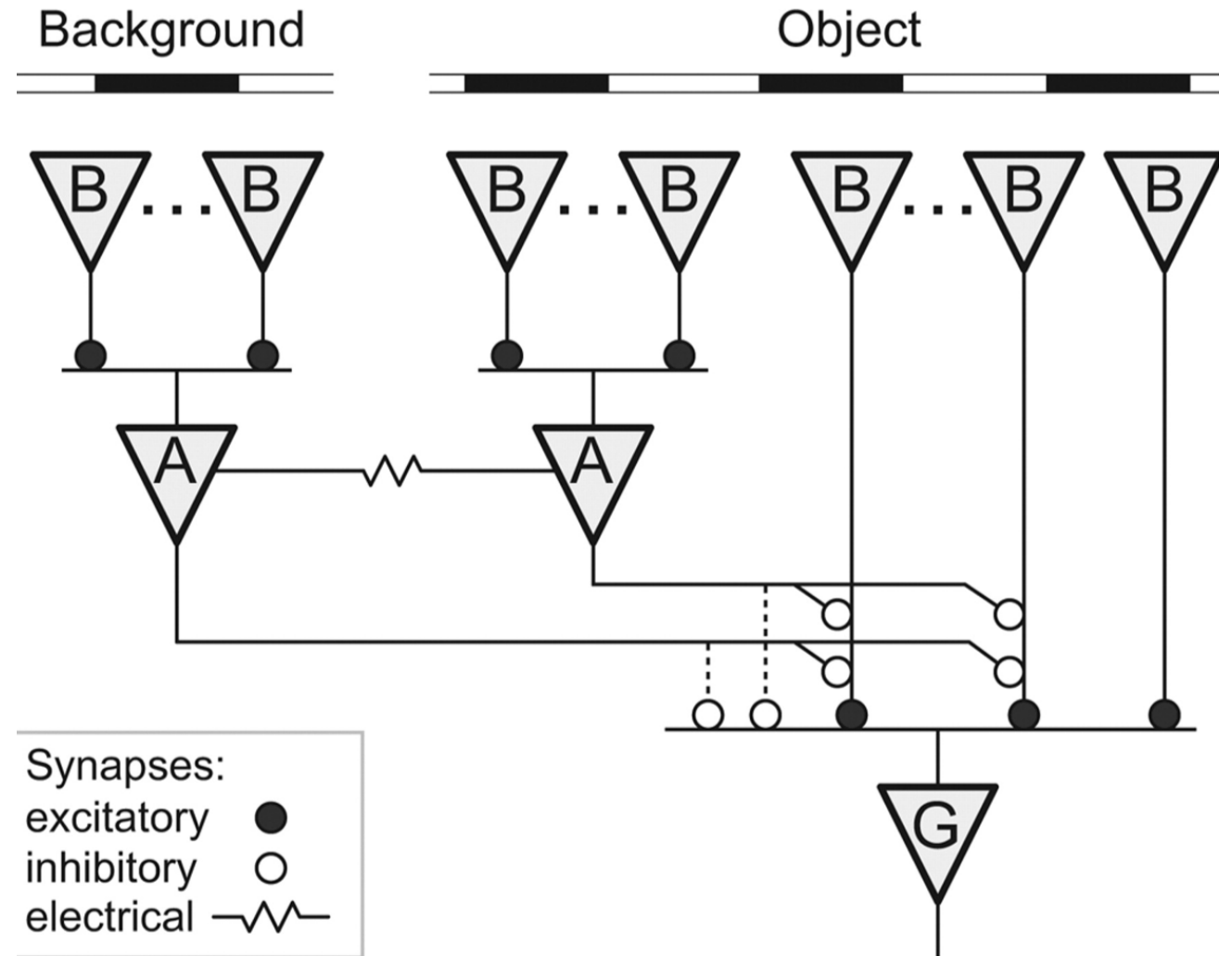


Background & Object moving

Retinal circuit related to motion

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

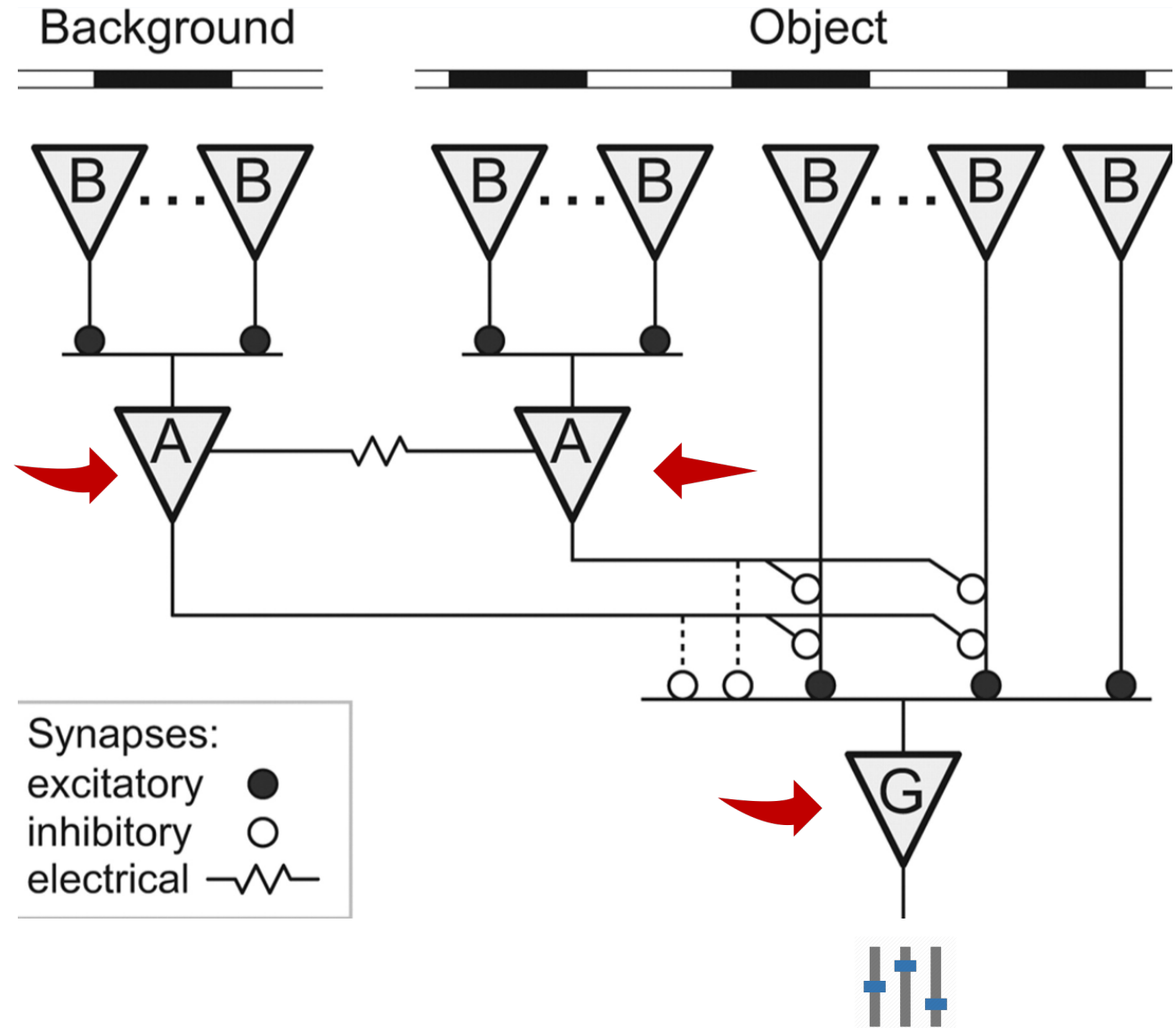
Background region: Inhibitory input to the ganglion cell (G) from amacrine cells (A).



CNO effect on the circuit

DREADDs on :

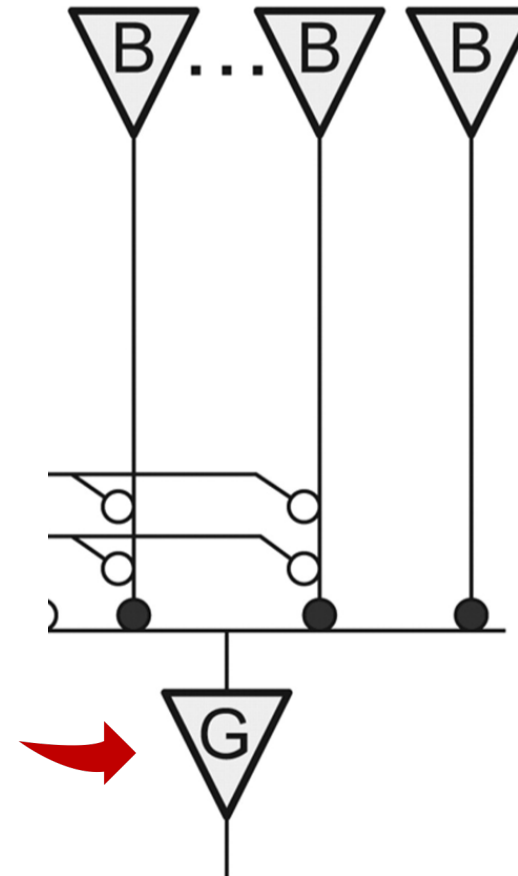
- Amacrine cells (ACs) and/or
- Ganglion cells (RGCs)



CNO effect on the circuit

DREADDs on Ganglion cells (RGCs)

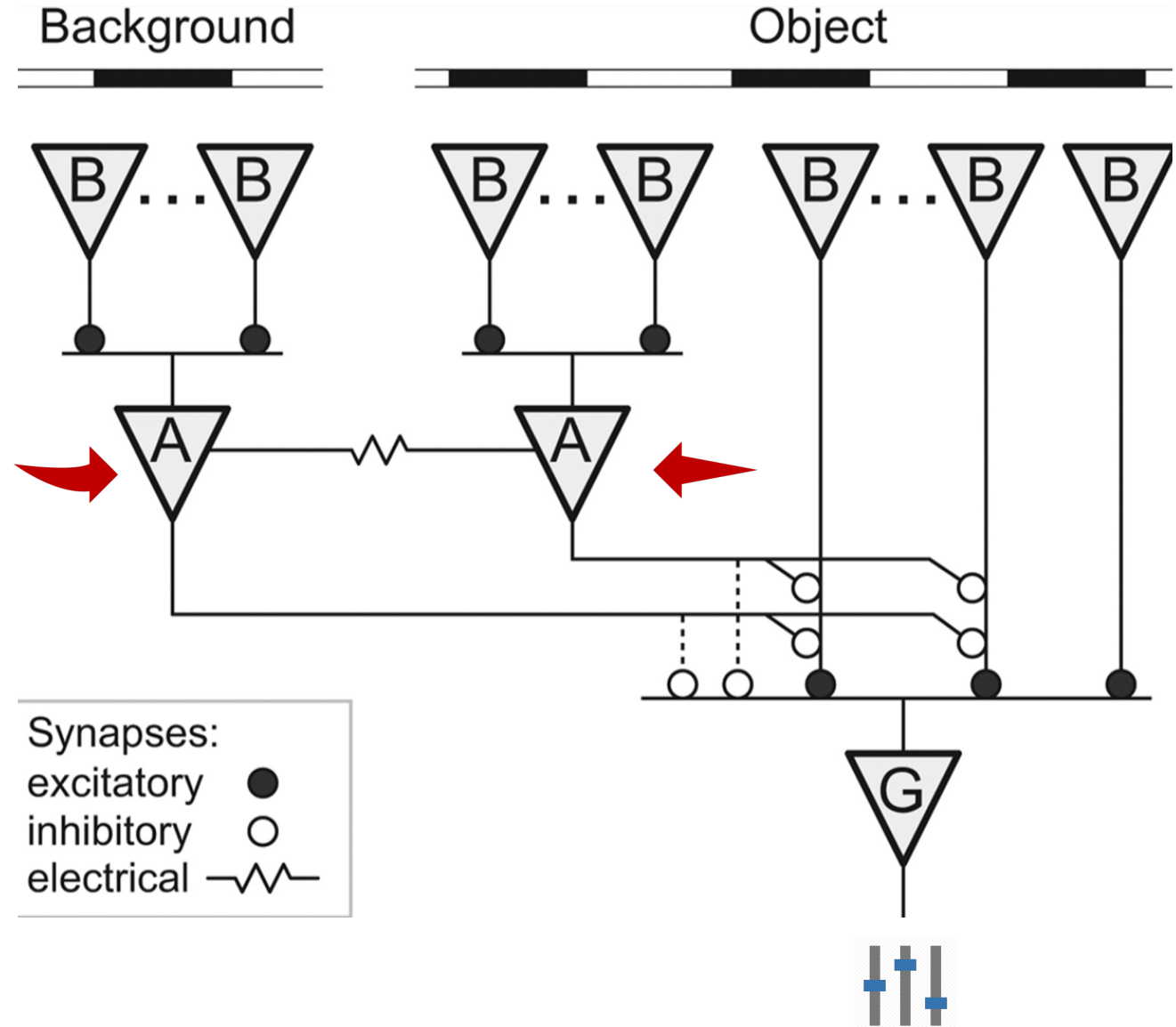
- If excitatory, the neuronal activity will increase
- If inhibitory, the neuronal activity will decrease



CNO effect on the circuit

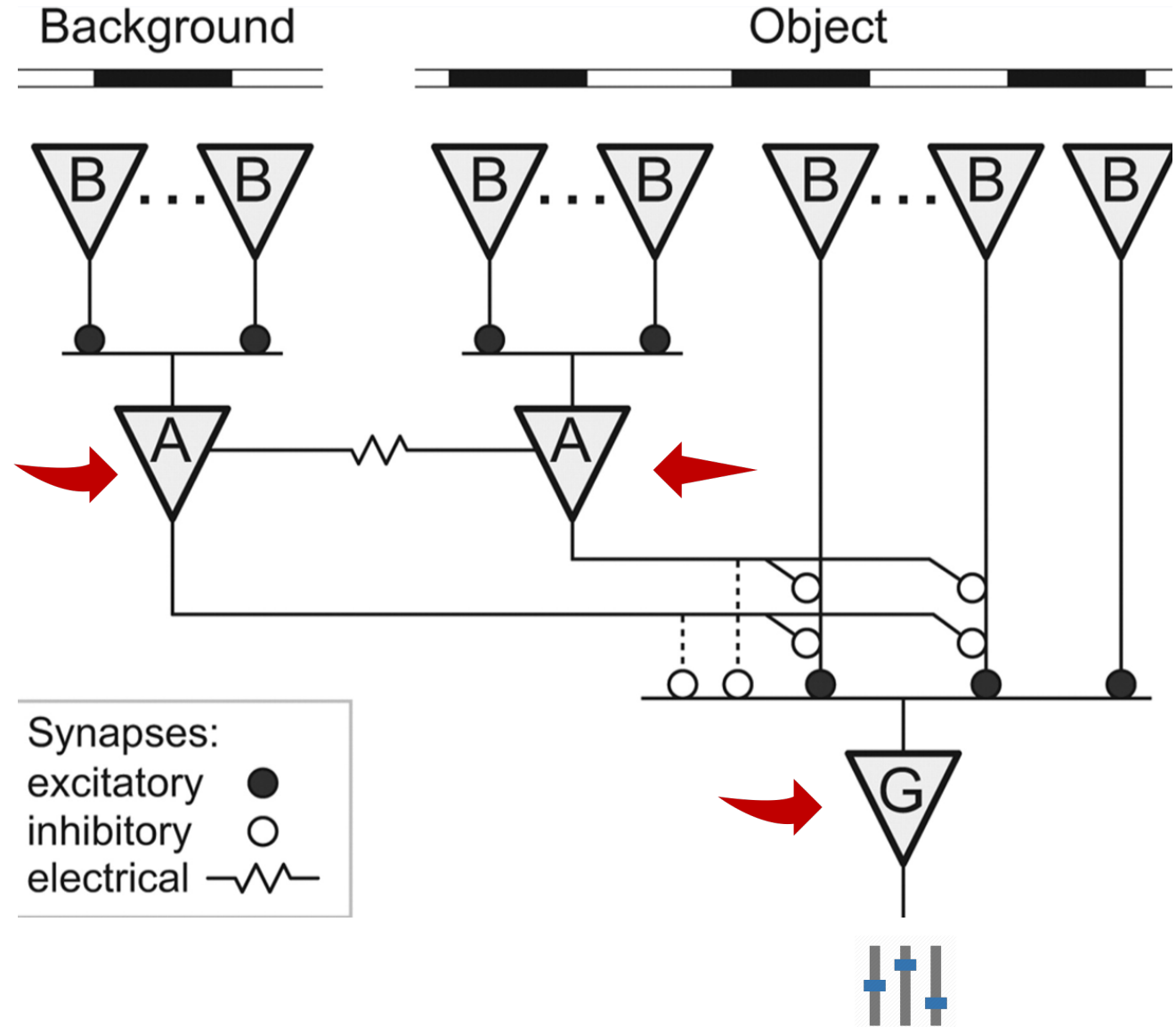
DREADDs on Amacrine cells (ACs):

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

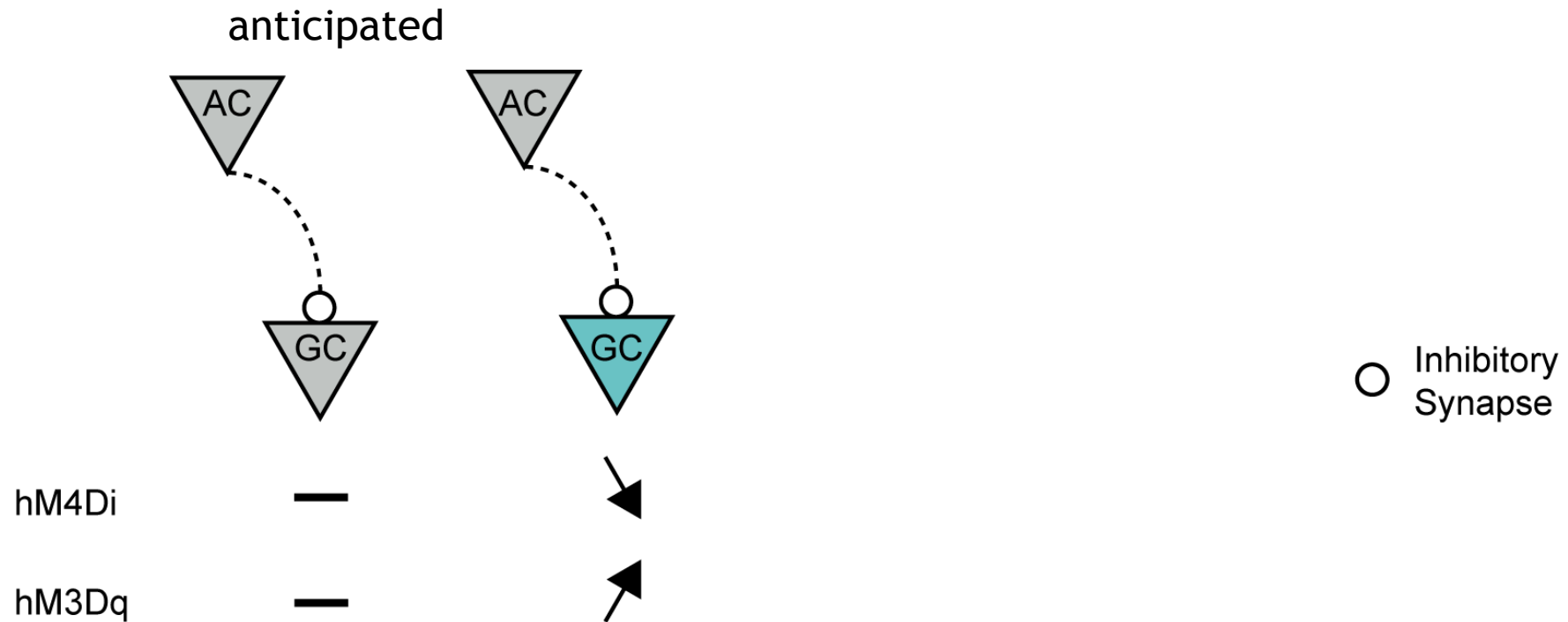


CNO effect on the circuit

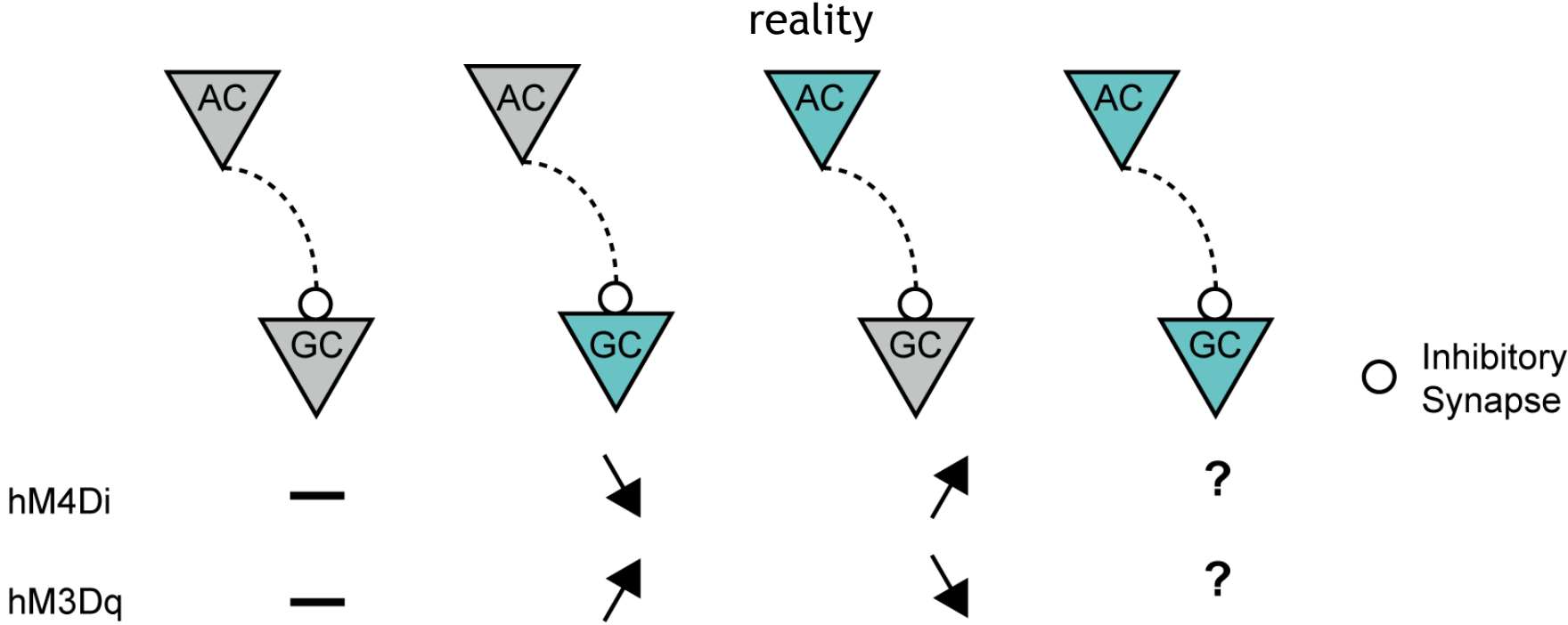
DREADDs on : ACs AND RGCs



Electrophysiological characterisation of Scnn1a and Grik4 DREADD RGCs

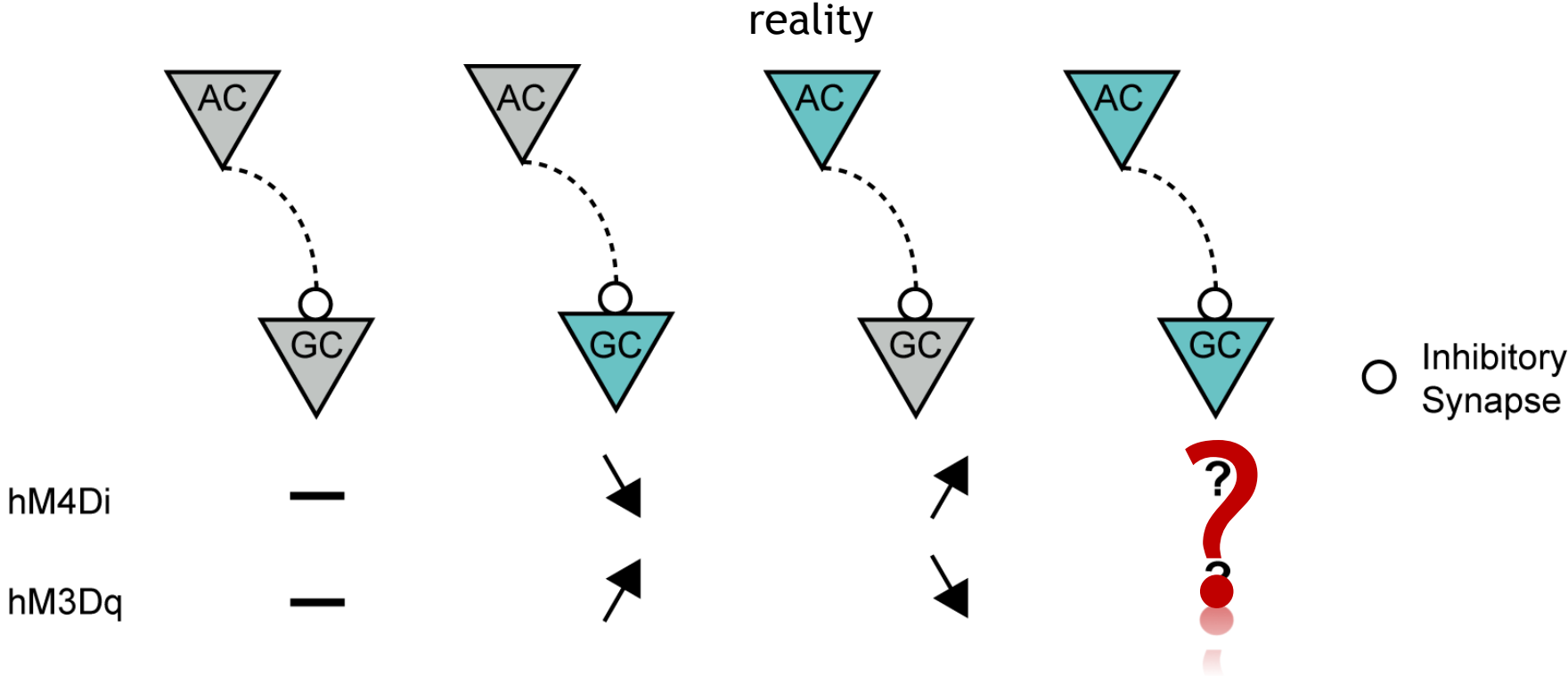


Electrophysiological characterisation of Scnn1a and Grik4 DREADD RGCs



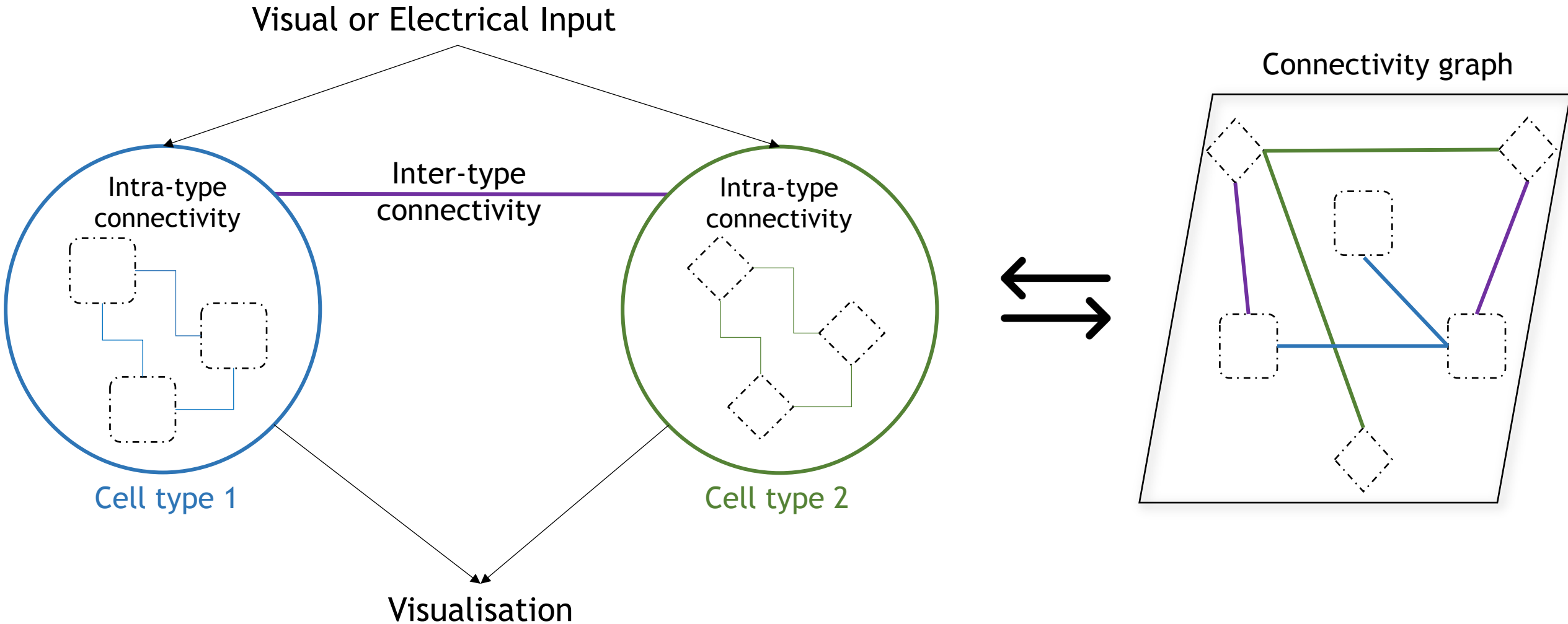
DREADDs in ACs makes the interpretation of functional results from DREADD-expressing RGCs more challenging.

Electrophysiological characterisation of Scnn1a and Grik4 DREADD RGCs

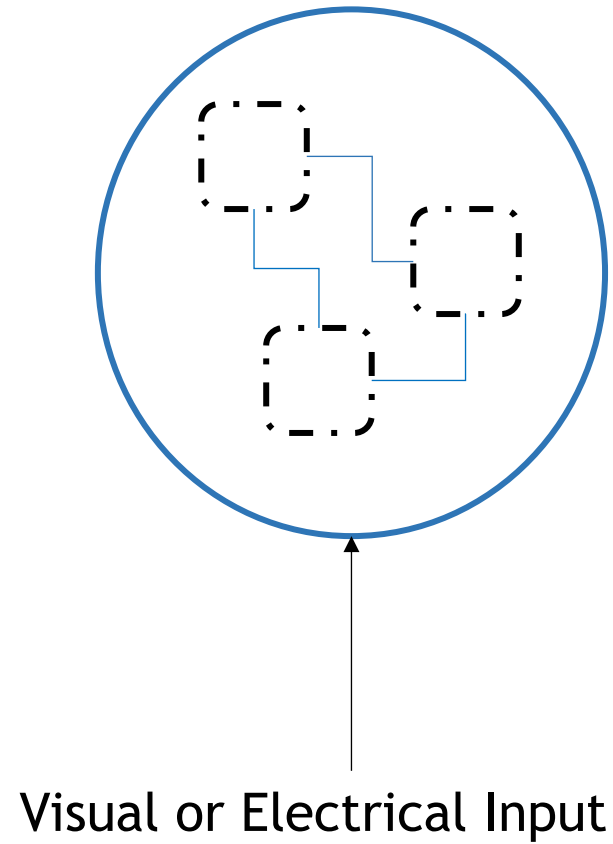


Solution: Study it numerically

General structure

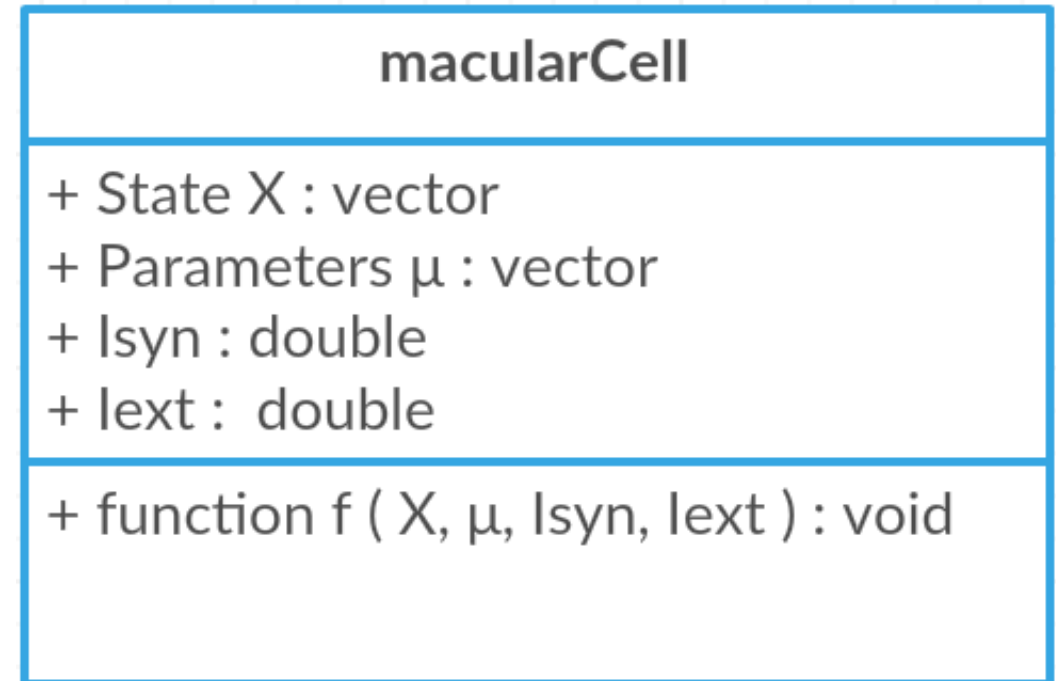


Basic building blocks - cell



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

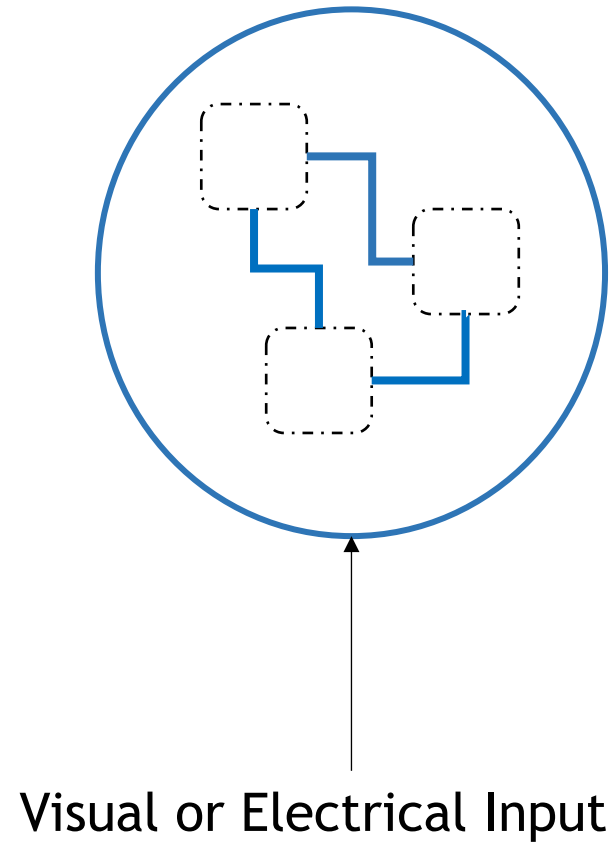
macularCell
+ State X : vector + Parameters μ : vector + Isyn : double + Iext : double
+ function $f (X, \mu, I_{syn}, I_{ext}) : void$

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
- ✓ **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

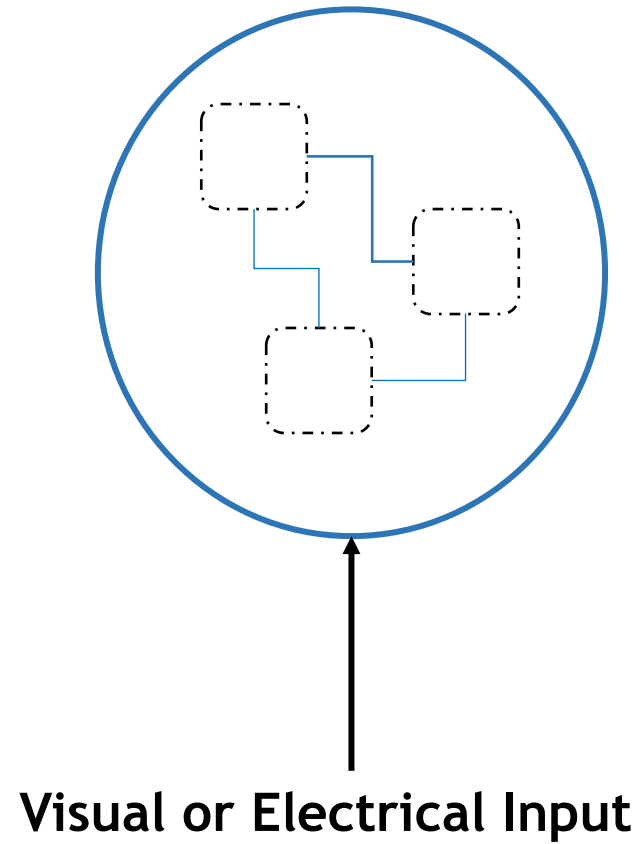
macularSynapse

+ Variables X : vector
+ Parameters μ : vector

+ computeSynapticCurrent ($X, \mu, \text{pre}, \text{post}$) : 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



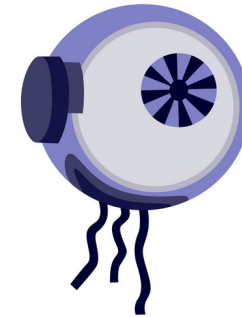
Visual Input



Virtual Retina module

- ✓ Emulate the outer plexiform layer (OPL) current

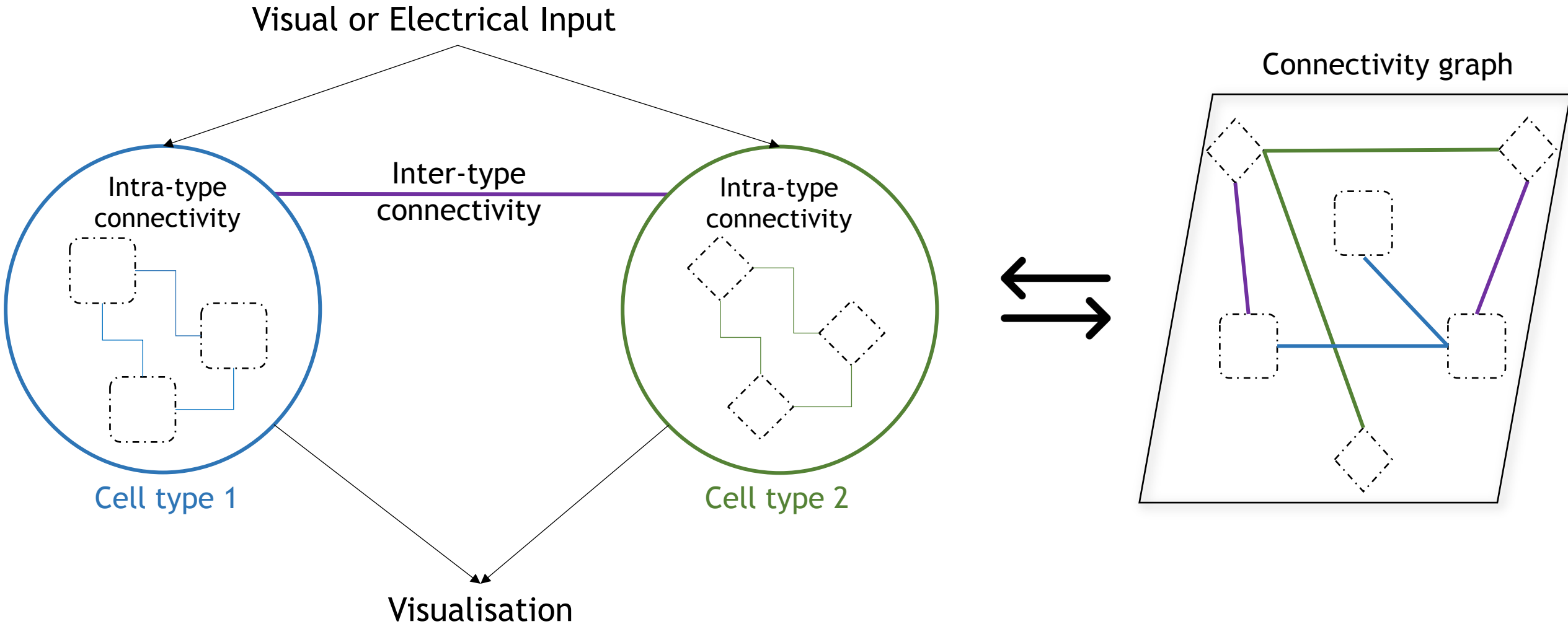
A.Wohrer et al., 2009



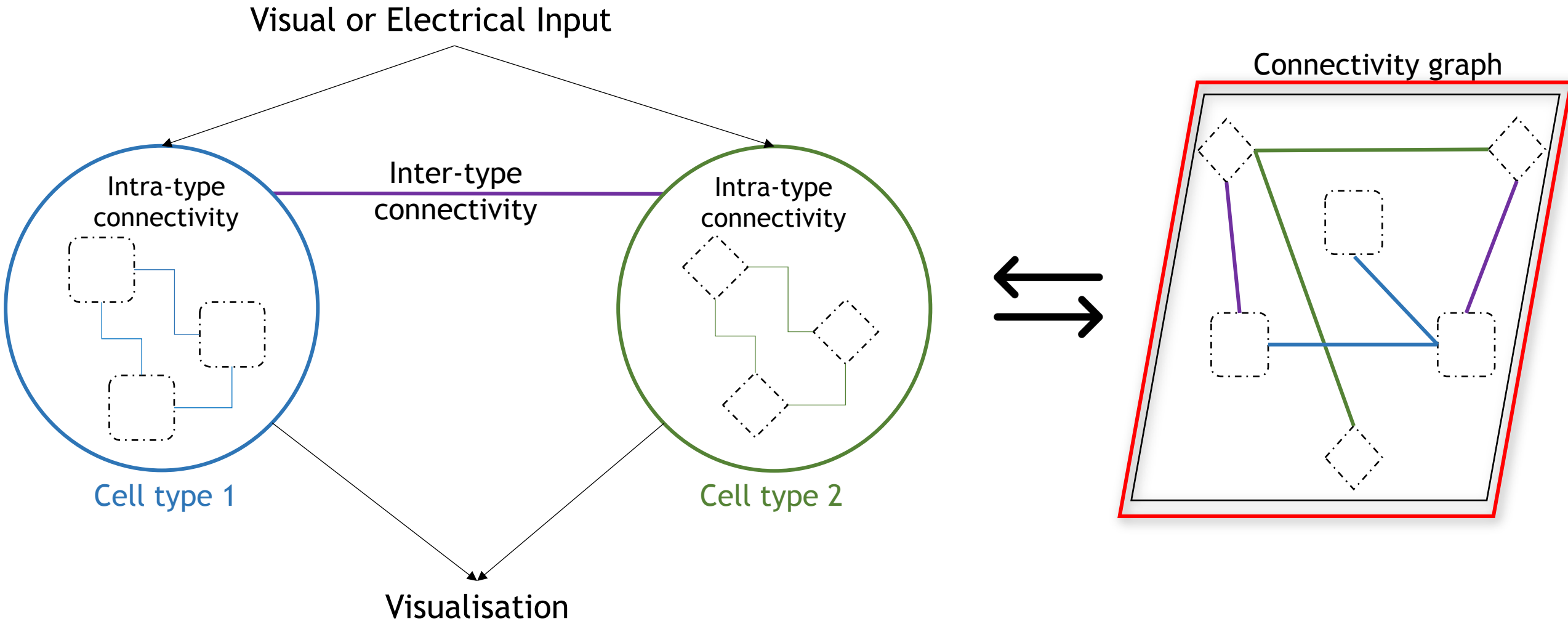
Retinal prosthesis

- ✓ Emulate the electric current provided by an electrode

General structure



General structure



Graph

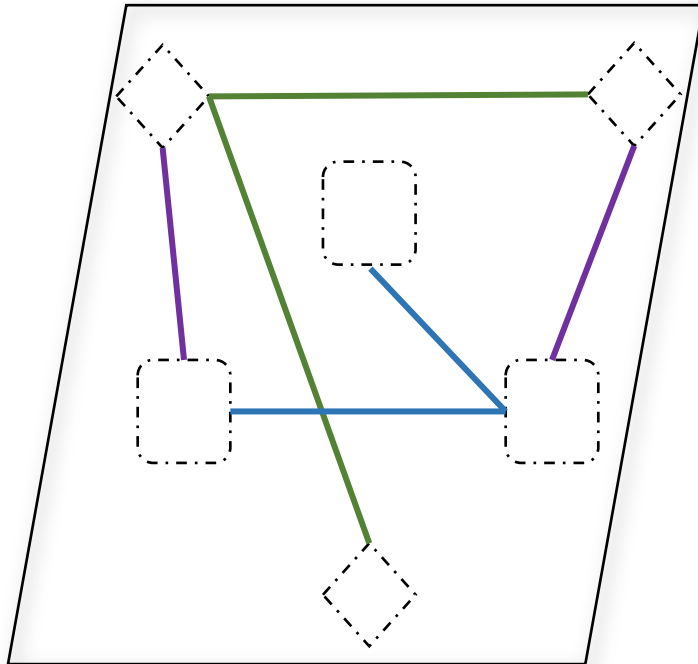
macularGraph

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

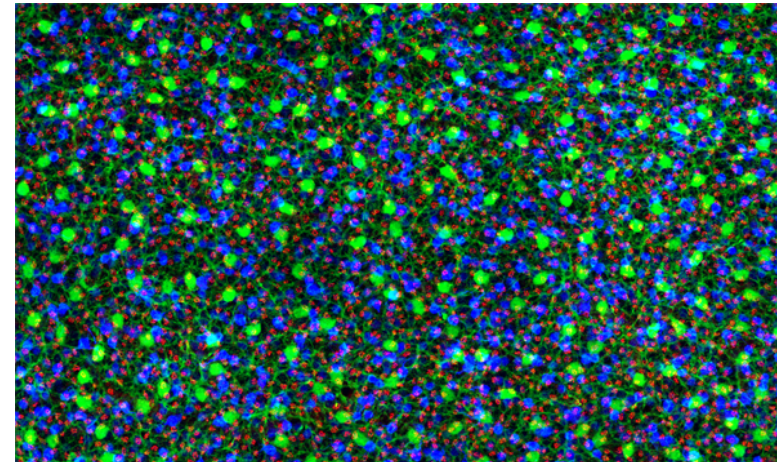
- ✓ Cell types
- ✓ Synapse types
- ✓ Cell coordinates
- ✓ Synapse indices

Graph

Connectivity graph



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



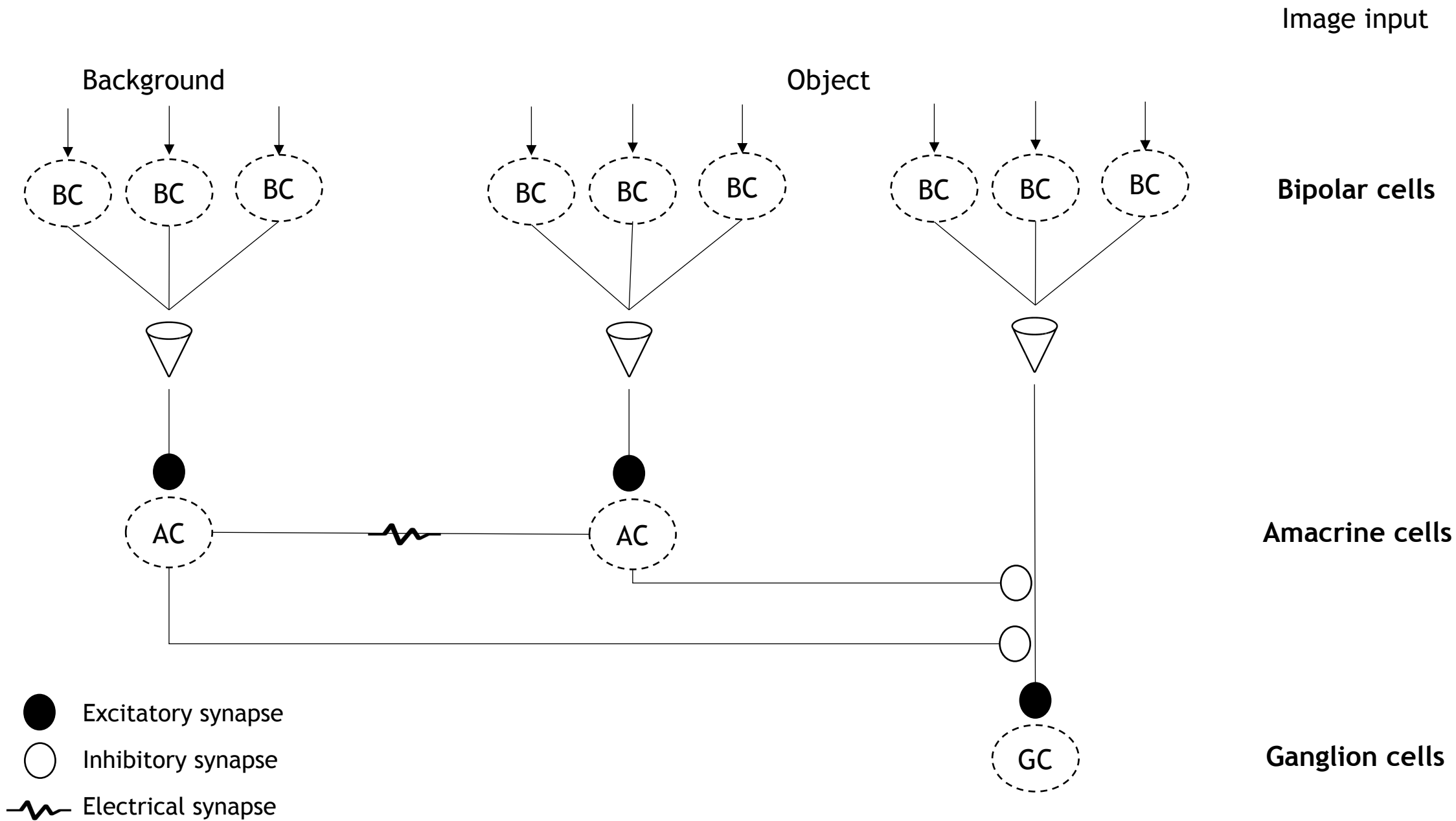


Image input

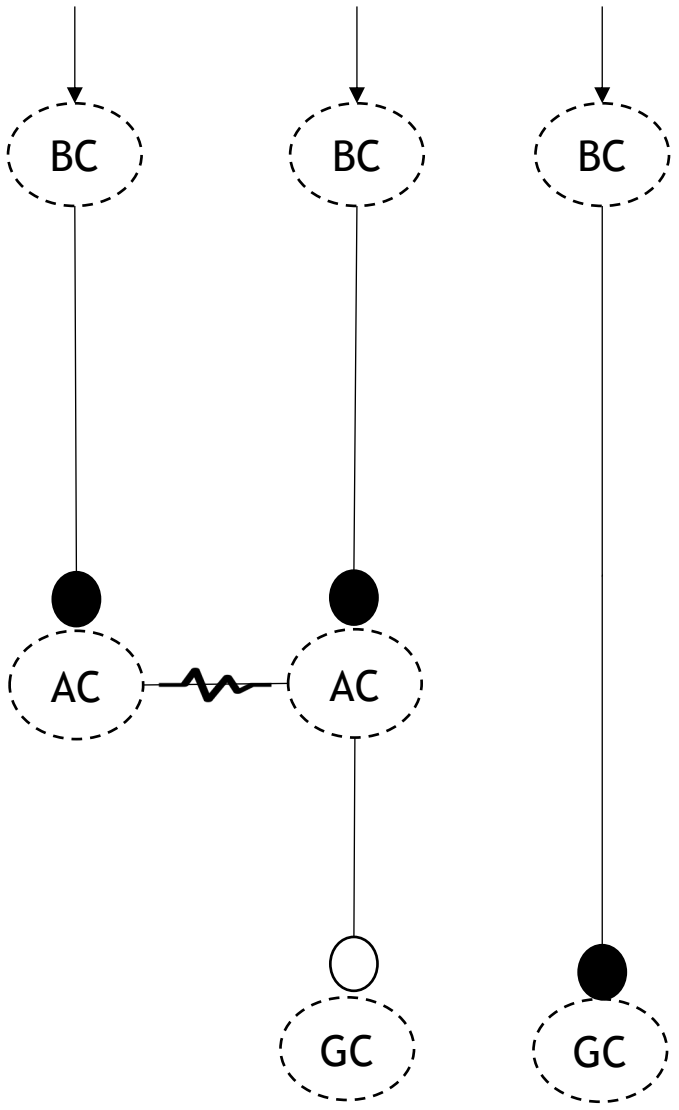
Background

Object

Bipolar cells

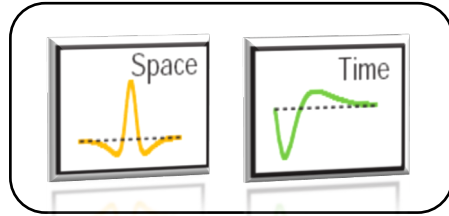
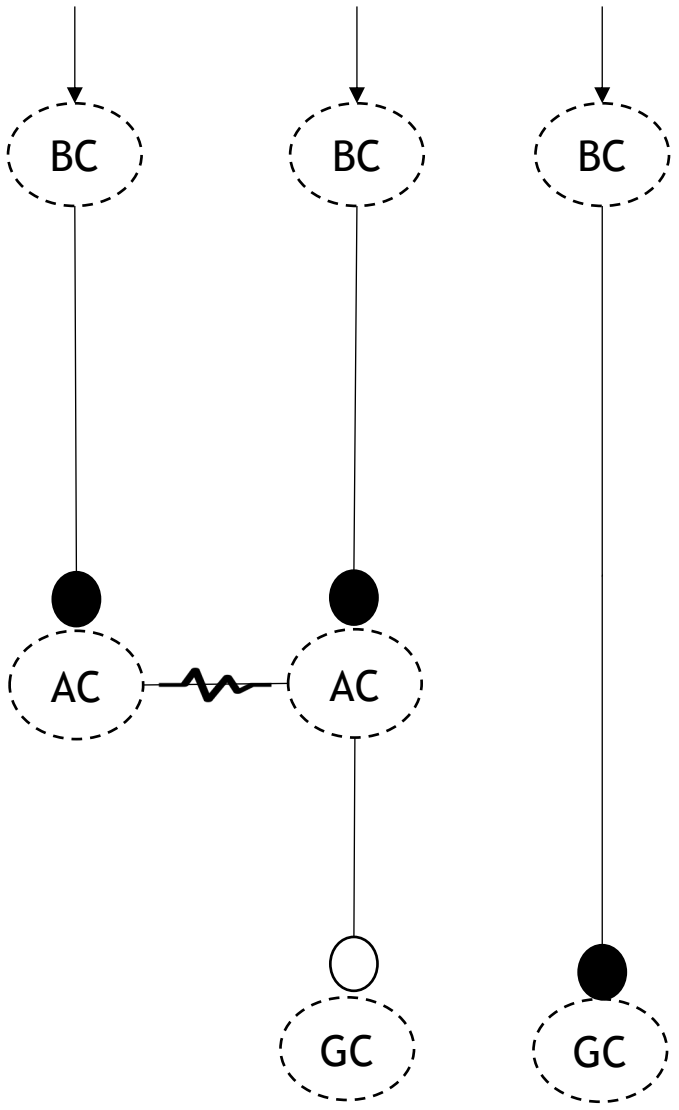
Amacrine cells

Ganglion cells



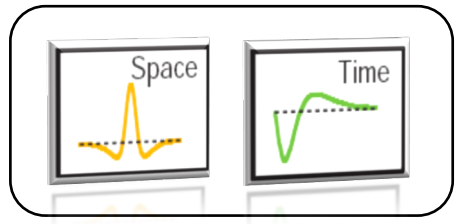
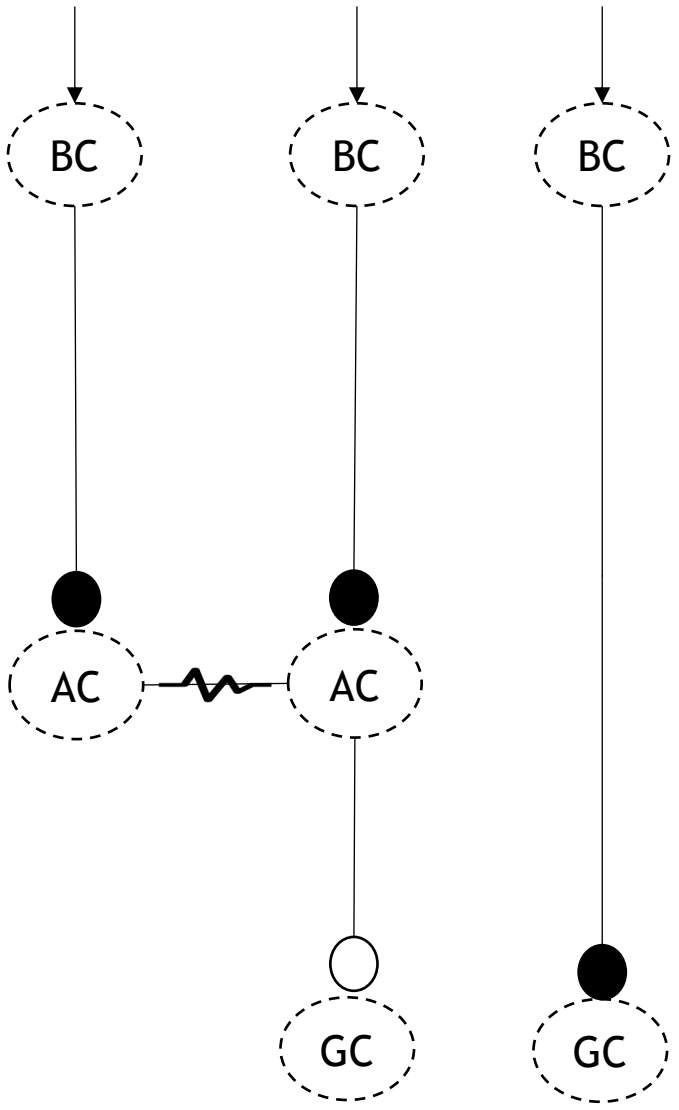
● ○ Chemical synapse

— Electrical synapse



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

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



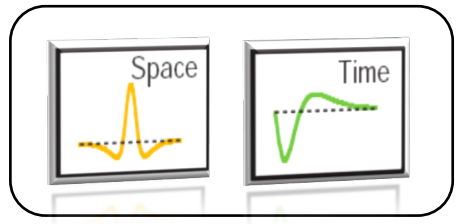
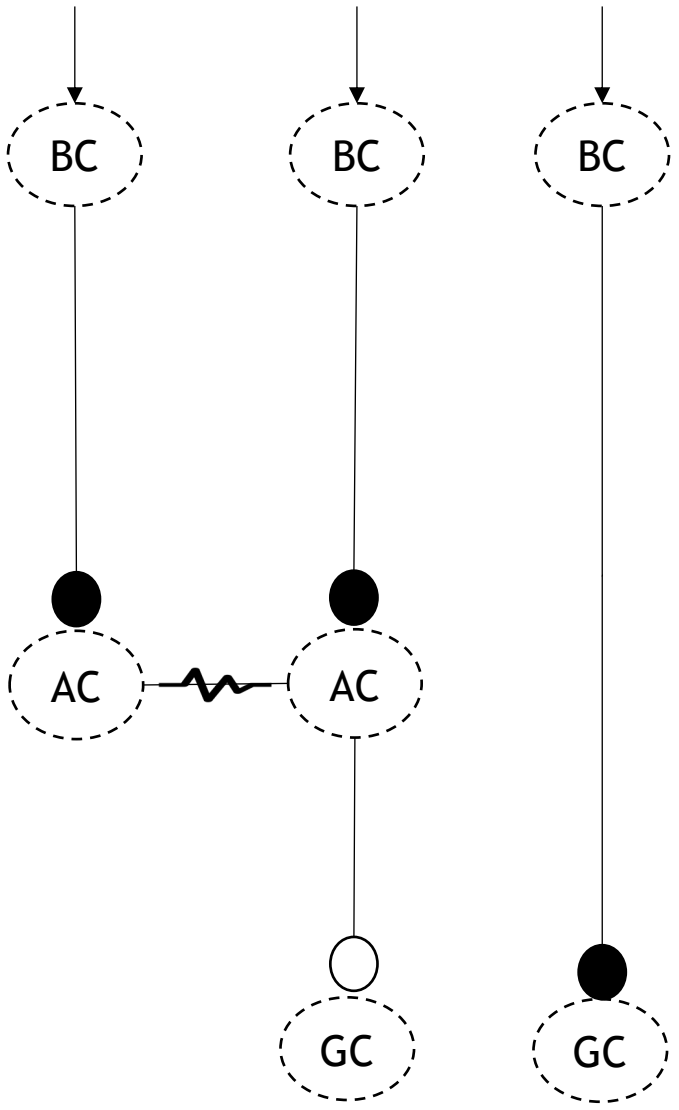
● ○ Chemical synapse
 ~~~~~ Electrical synapse

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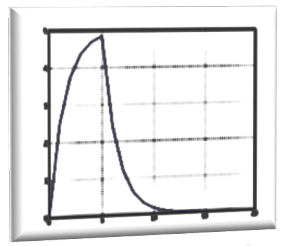
$$\int (S * K)(x, y, t)$$

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

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



● ○ Chemical synapse  
 ~~~~~ Electrical synapse



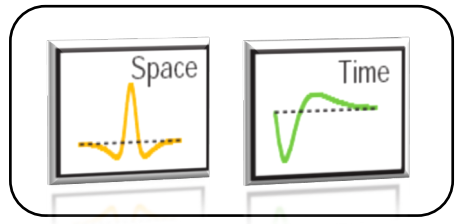
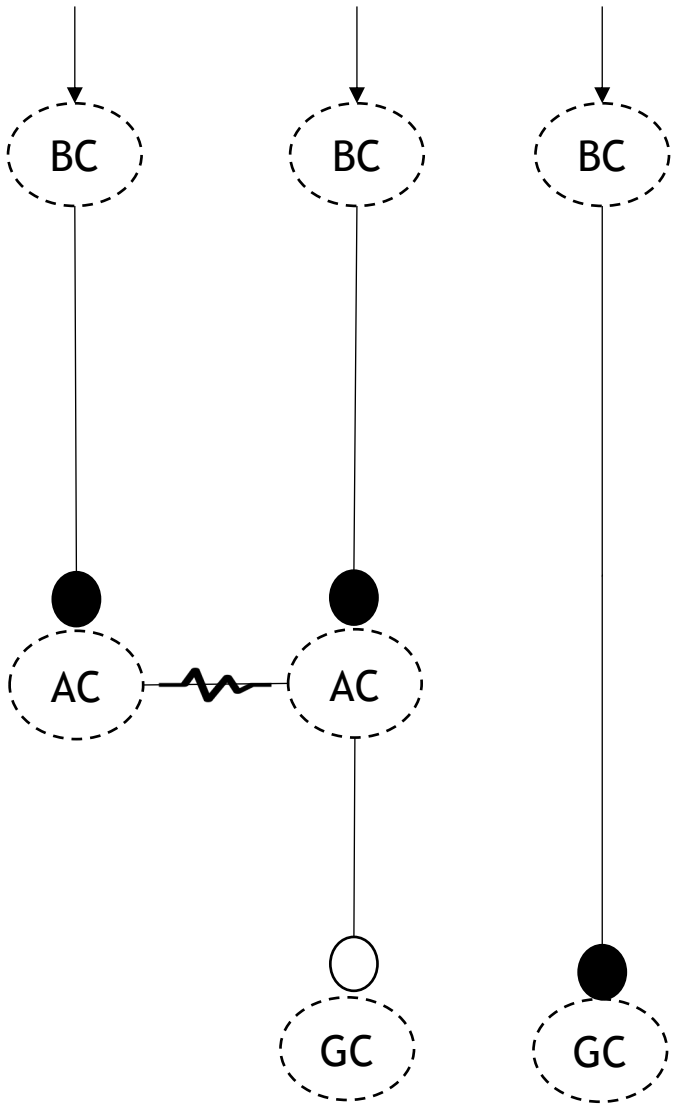
$$K(x, y, t) = K_S(x, y)K_T(t)$$

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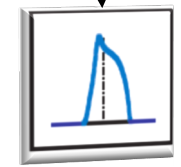
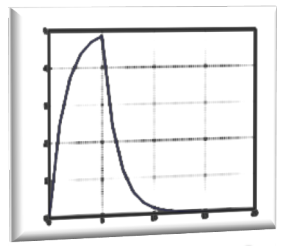
$$I_{syn} = -g_{syn} (V_{post} - E_{syn})$$

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

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



● ○ 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  $gA * A^{**2} / (gammaA + A^{**2})$


All

Acetylcholine


+ New


 File


 Themes


 Choose Theme >

Model synaptic current


Cancel Save



Ganglions  
Video

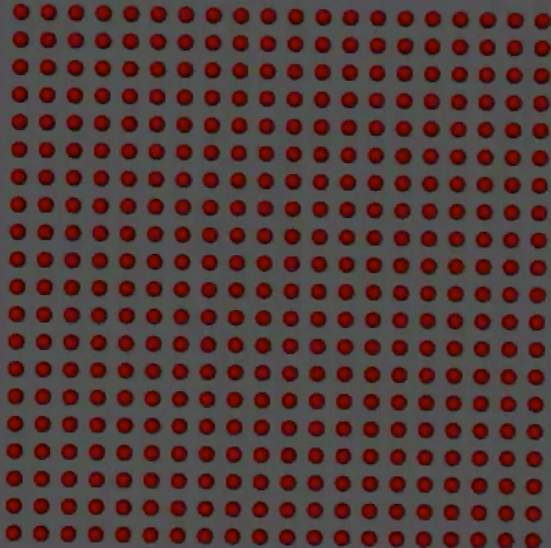


**Simulator**



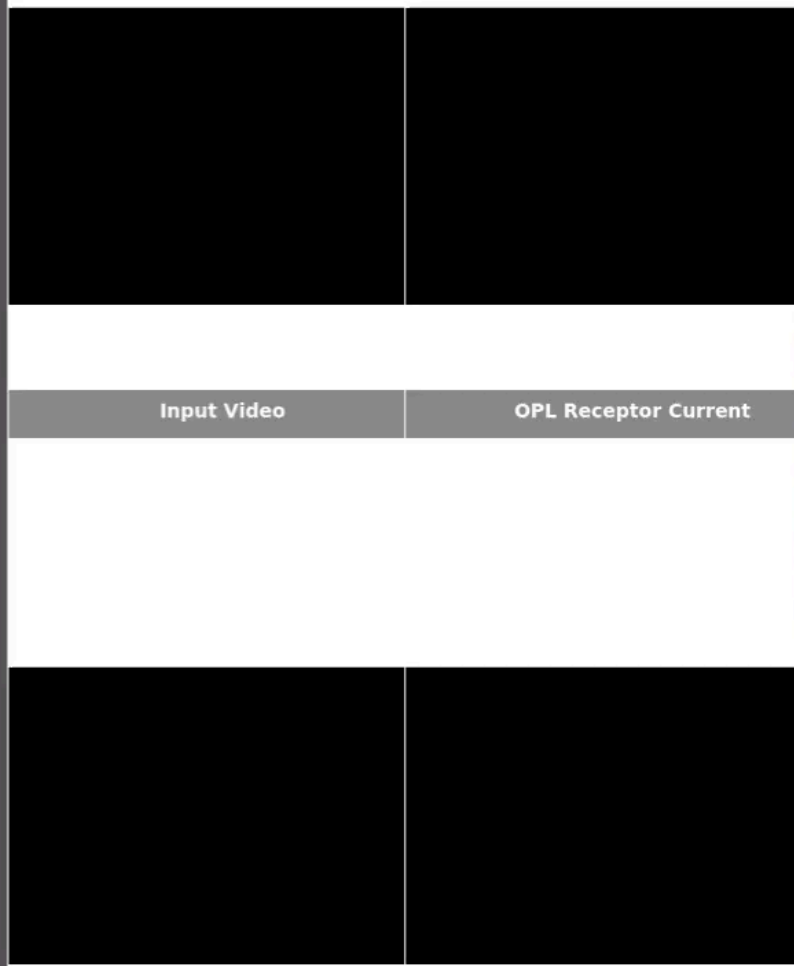
Graph Generator

0.00 0.00 0.00 0.00 0.00



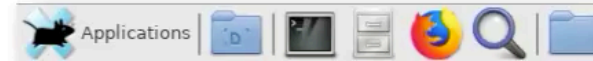
Canvas - 2

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**

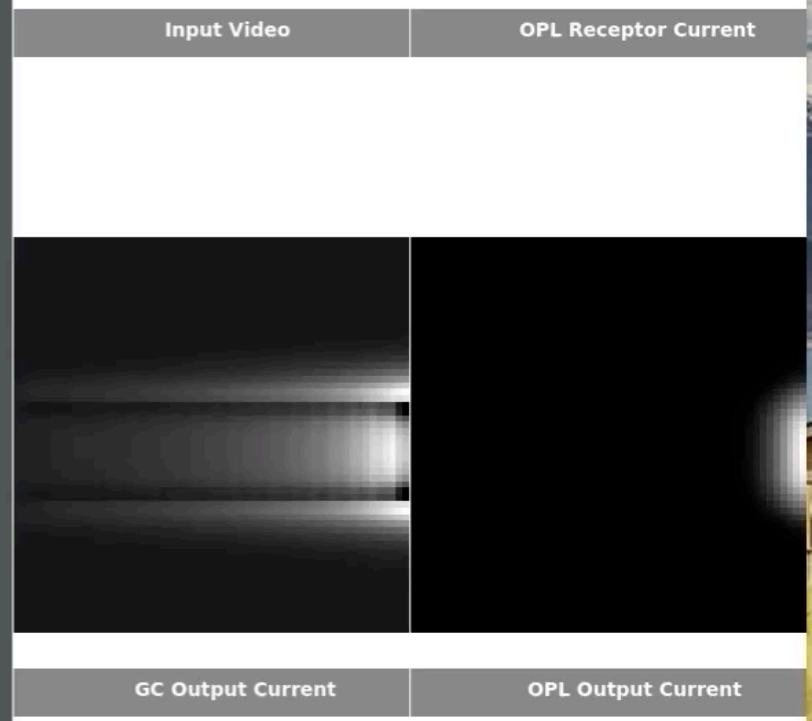
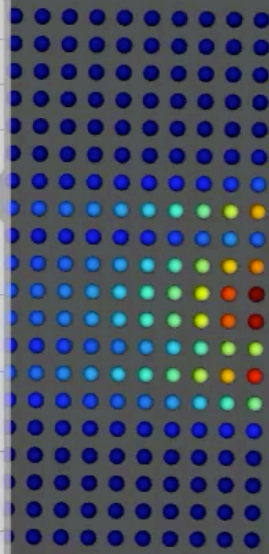
Save/Restore parameters

Save frequency **0**

Model **Prosthesis**

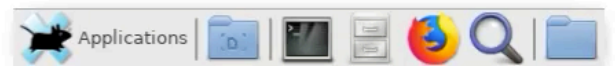
Parameters

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



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 showing more diffuse fluorescence. The overall aesthetic is scientific and modern.

**Thank you!**

**Questions?**