



Probing retinal function with a multi-layered simulator

Evgenia Kartsaki, Bruno Cessac, Gerrit Hilgen, Evelyne Sernagor

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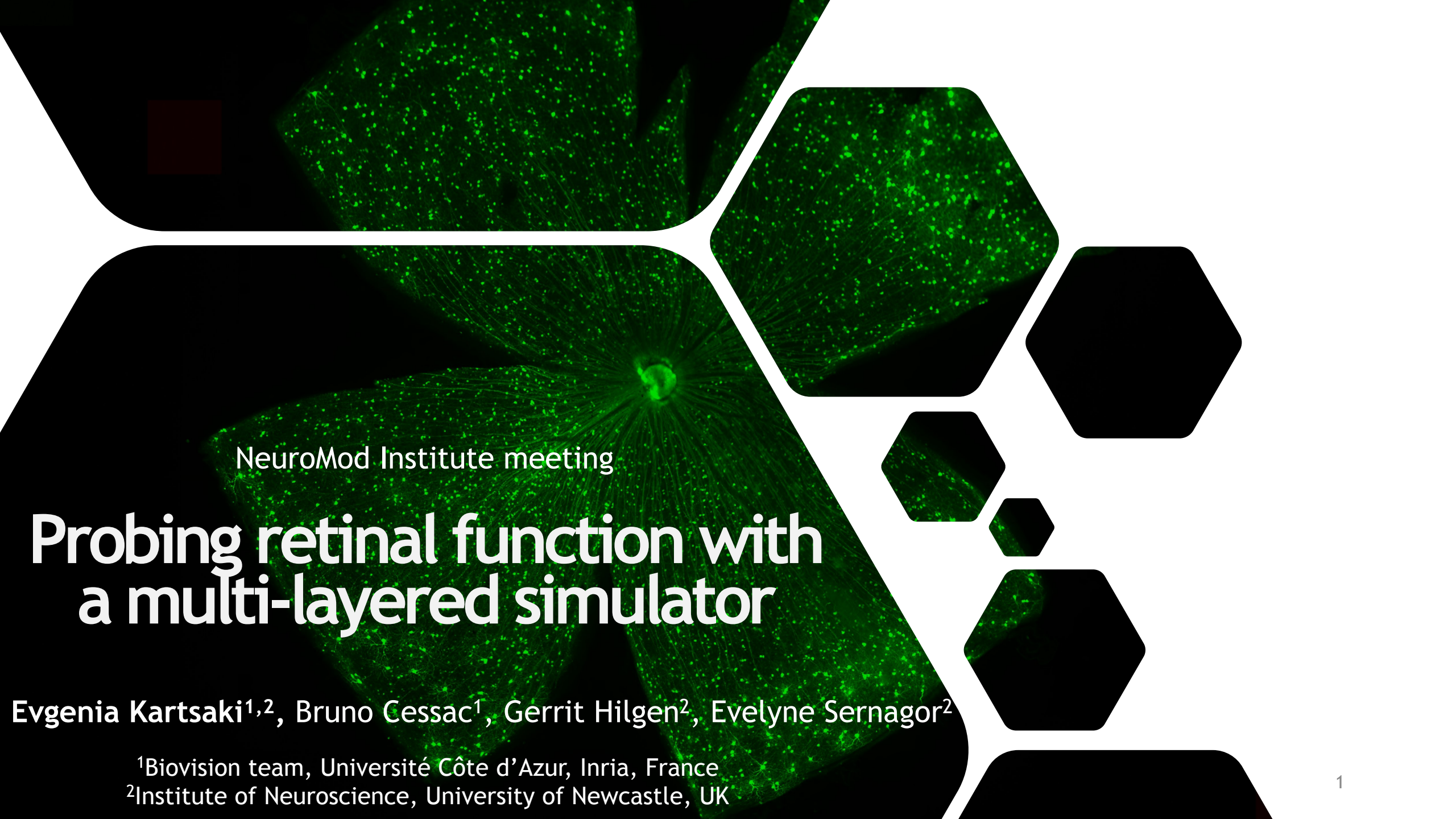
HAL Id: hal-02389086

<https://hal.science/hal-02389086>

Submitted on 2 Dec 2019

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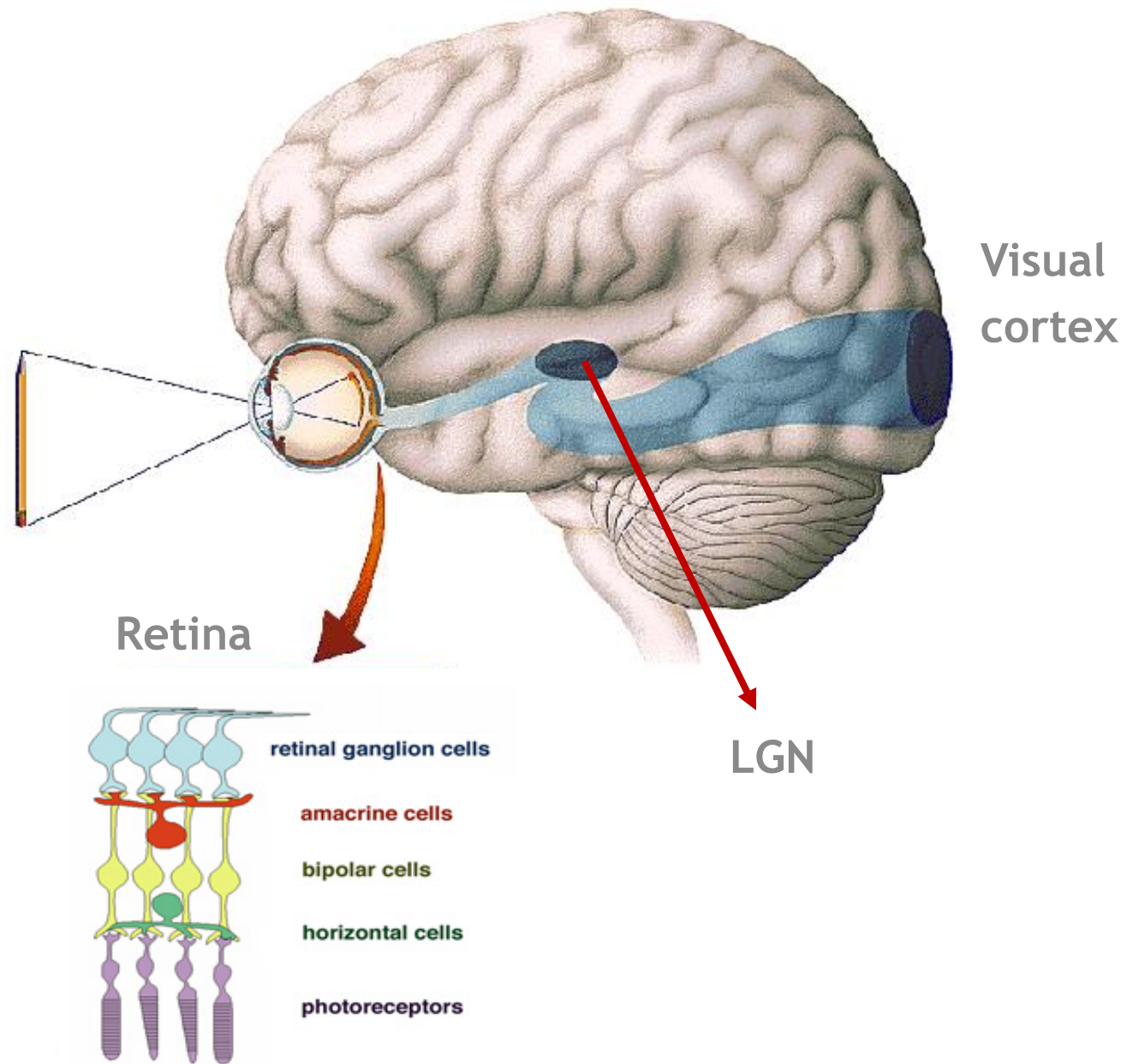
NeuroMod Institute meeting

Probing retinal function with a multi-layered simulator

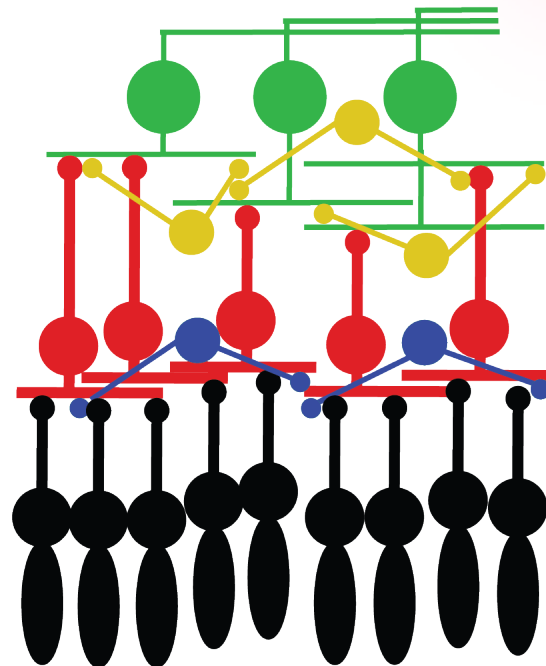
Evgenia Kartsaki^{1,2}, Bruno Cessac¹, Gerrit Hilgen², Evelyne Sernagor²

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

²Institute of Neuroscience, University of Newcastle, UK



Retinal visual flow



Retinal Ganglion Cells ●

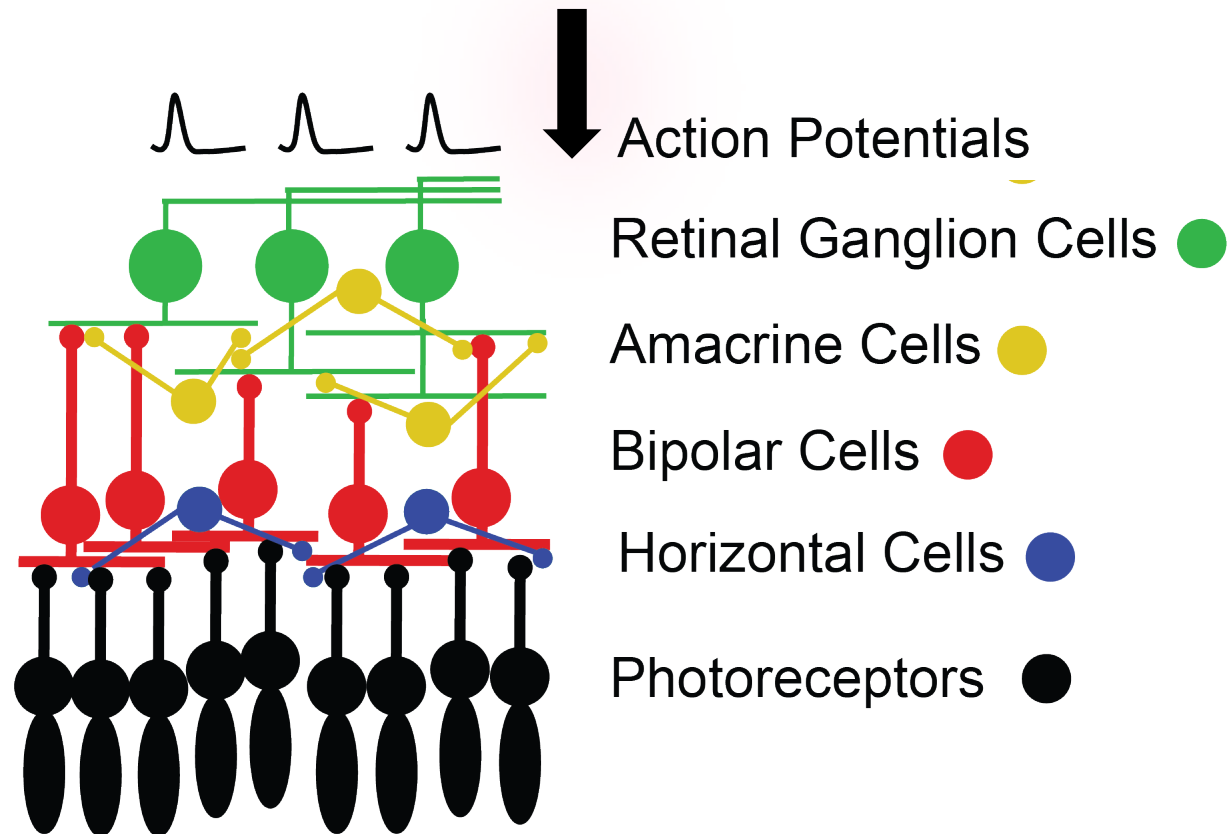
Amacrine Cells ●

Bipolar Cells ●

Horizontal Cells ●

Photoreceptors ●

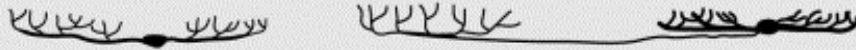
Retinal visual flow



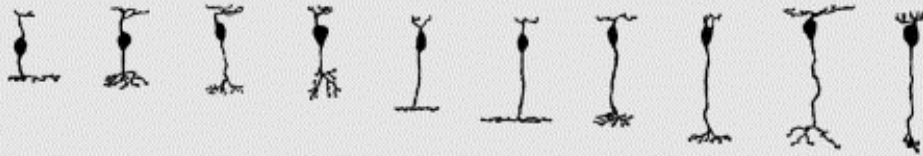
Photoreceptors



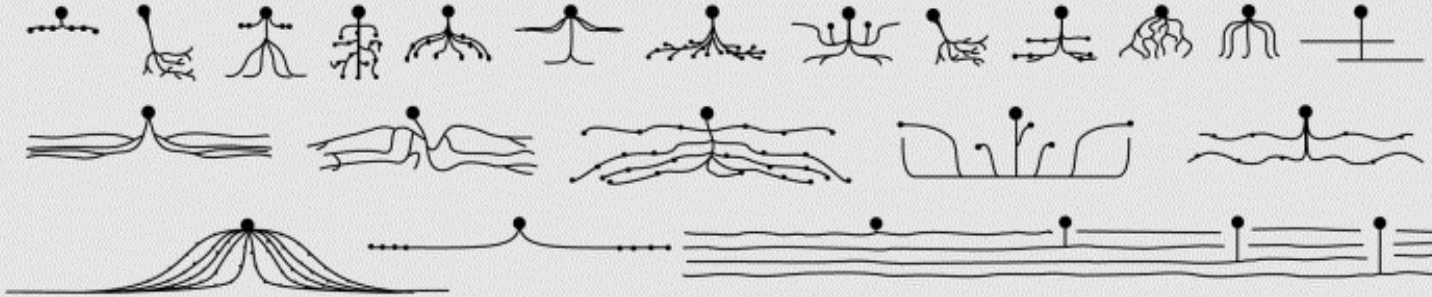
Horizontal cells



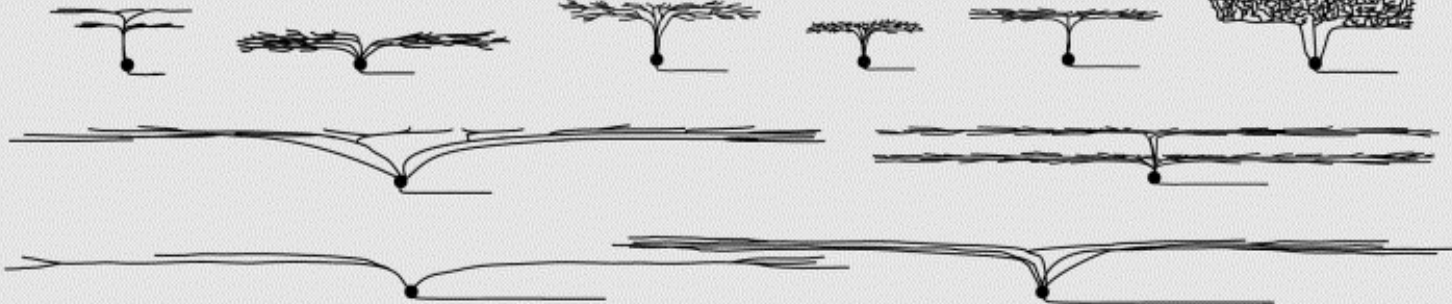
Bipolar cells



Amacrine cells



Ganglion cells



Retinal neurons inventory

Leverhulme funded project:

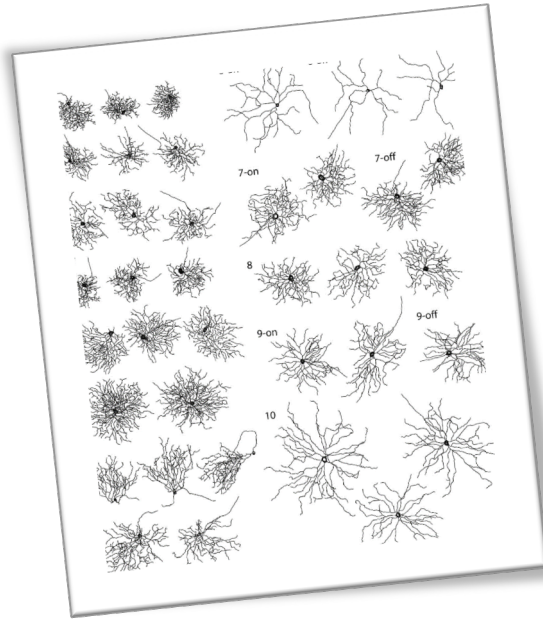
“A novel approach to functional classification of retinal ganglion cells”

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

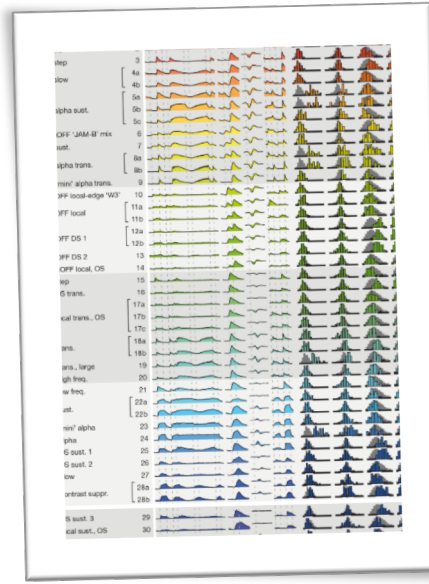
- pharmacogenetics
- large-scale retinal electrophysiology
- immunochemistry

☞ Understand their role in population encoding of complex visual scenes

Yet another RGC classification...



Coombs et al., 2006



Baden, Berens, Franke et al., 2016

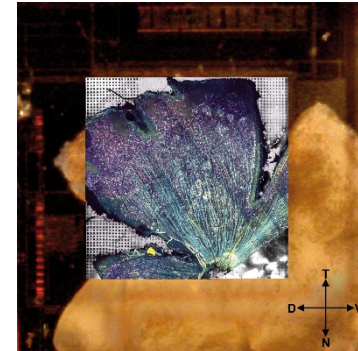
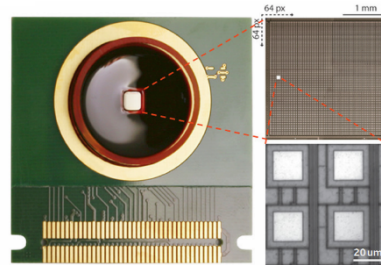


Martersteck, Hirokawa, Evarts et al., 2017

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

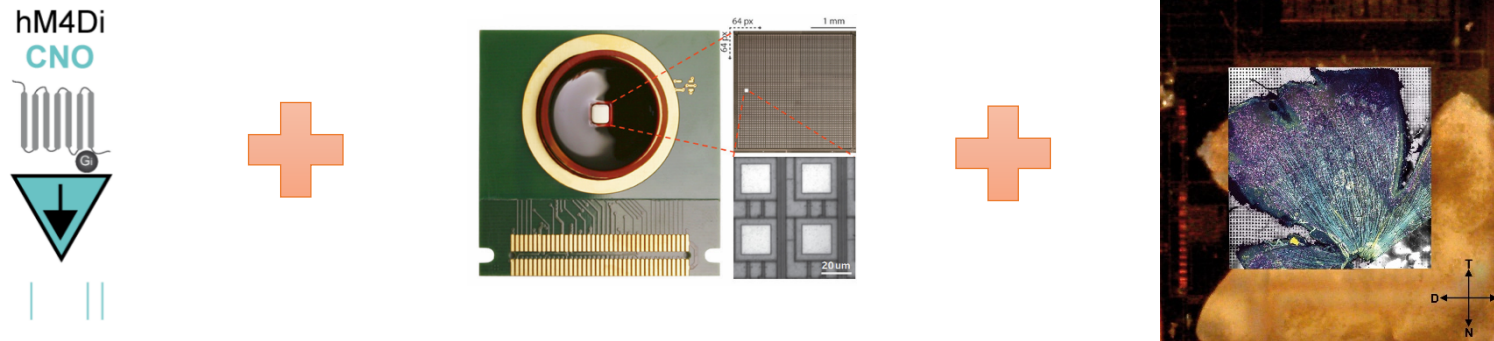
Aims

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



Aims

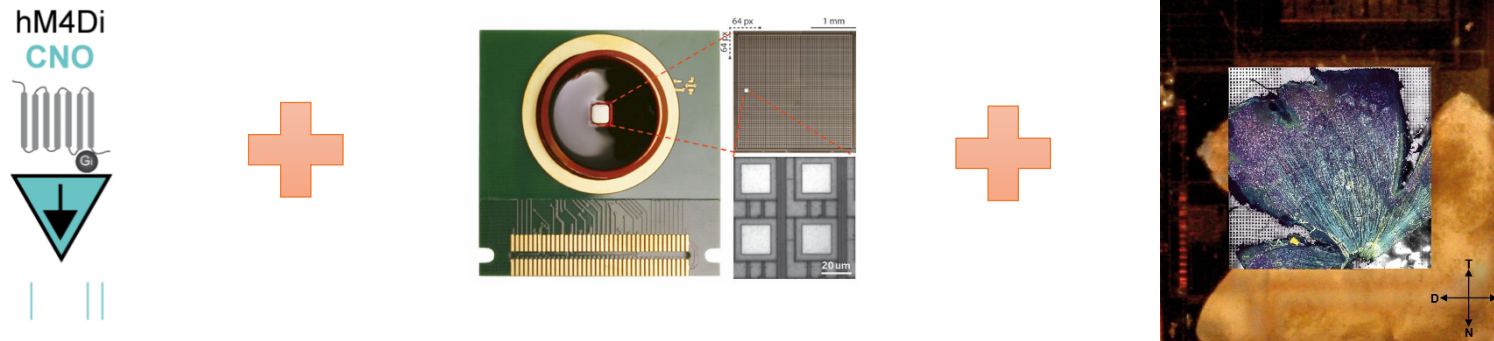
- Identify RGCs sharing a common gene expression by combining *pharmacogenetics*, large-scale high-density *electrophysiology* and *immunohistochemistry*



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

Aims

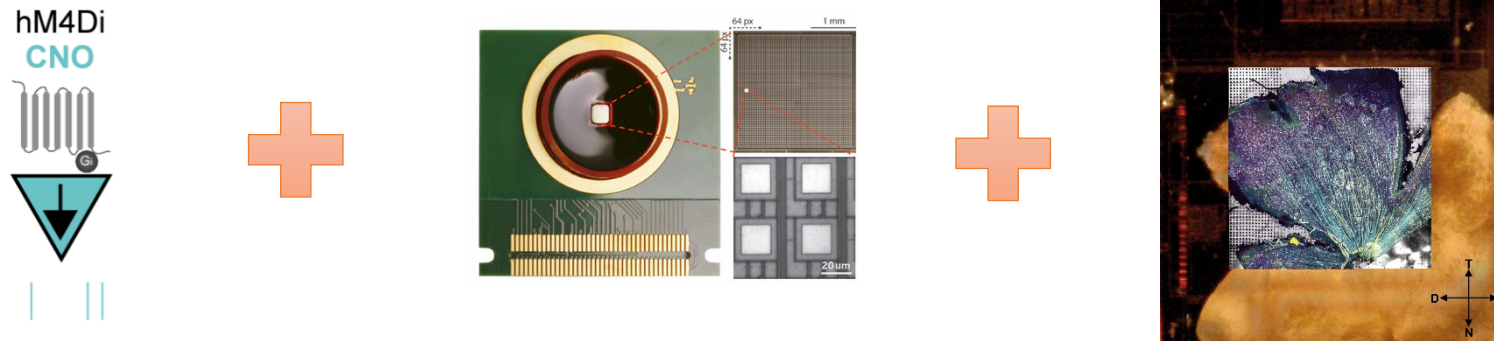
- Identify RGCs sharing a common gene expression by combining *pharmacogenetics*, large-scale high-density *electrophysiology* and *immunohistochemistry*



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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

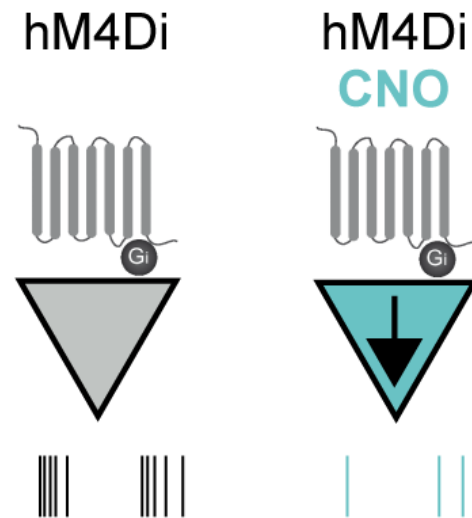
- Unravel how RGCs in these subgroups respond and interact to basic and complex visual scenes

Modelling

Numerical simulations

Pharmacogenetics - DREADD technology

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

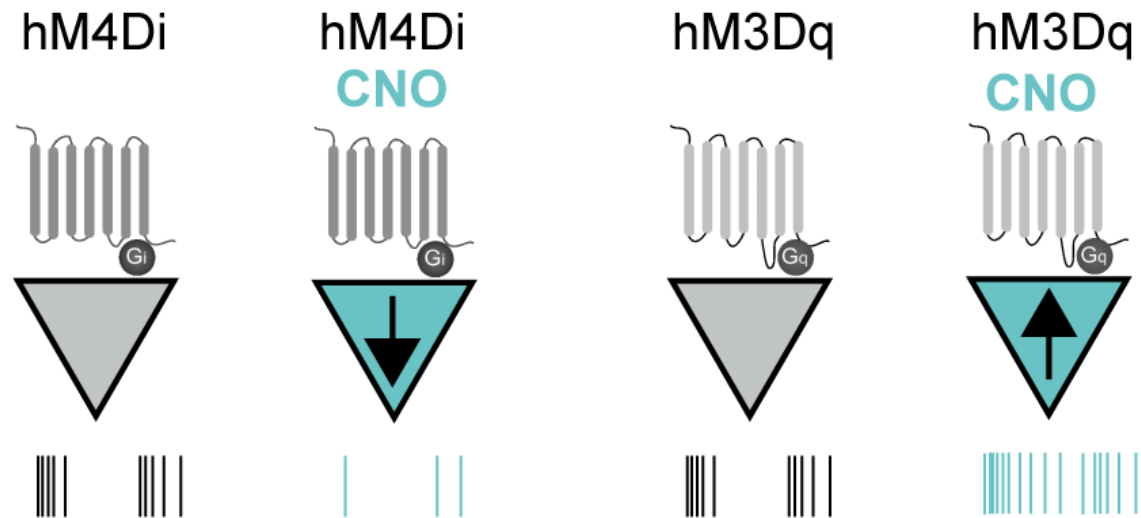


inhibitory DREADD



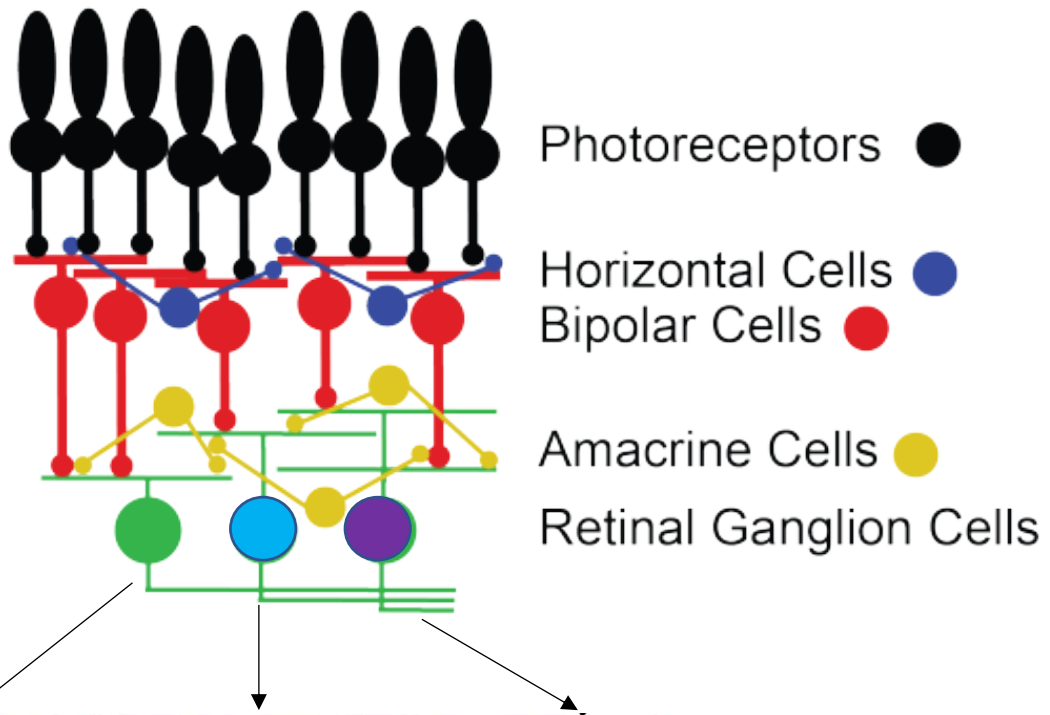
Pharmacogenetics - DREADD technology

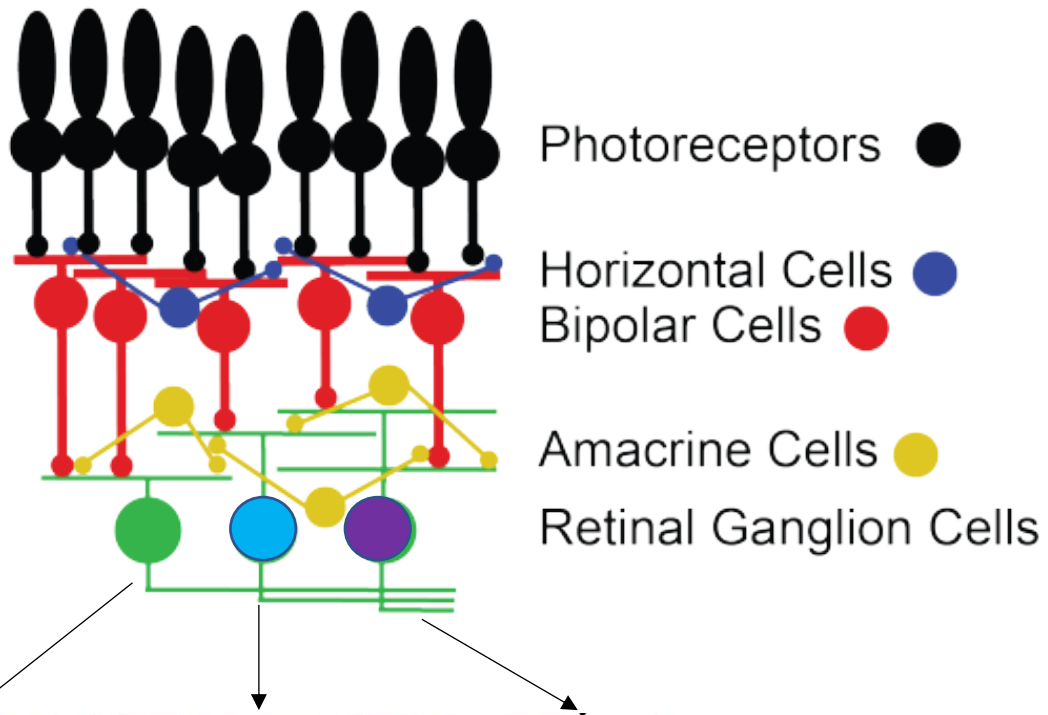
Designer **R**eceptors **E**xclusively **A**ctivated by **D**esigner **D**rugs



inhibitory DREADD

excitatory DREADD





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

Macular

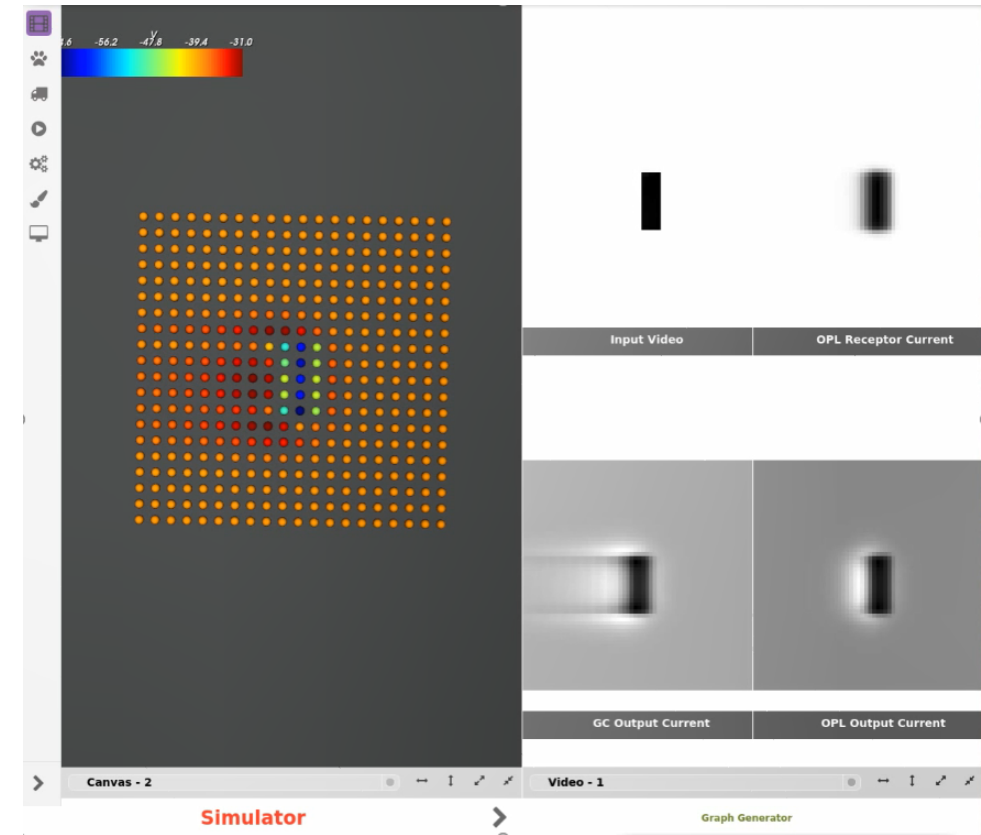
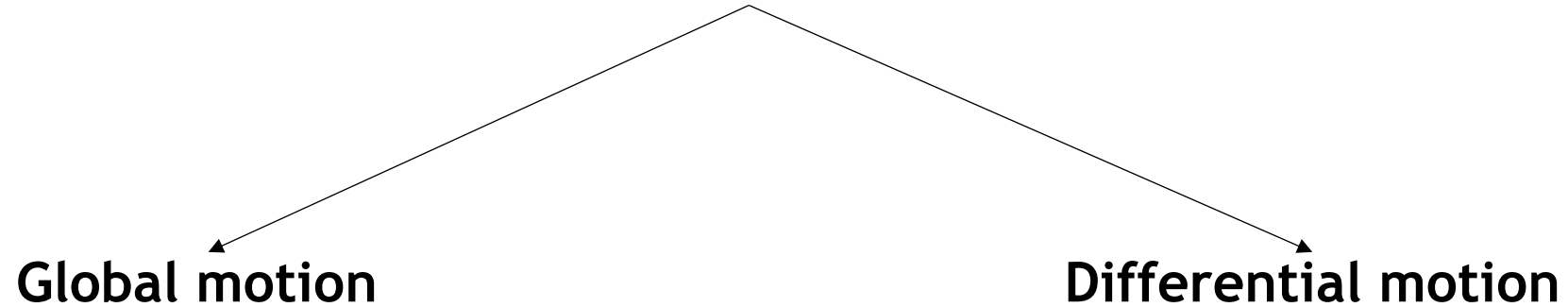


Image motion



```
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

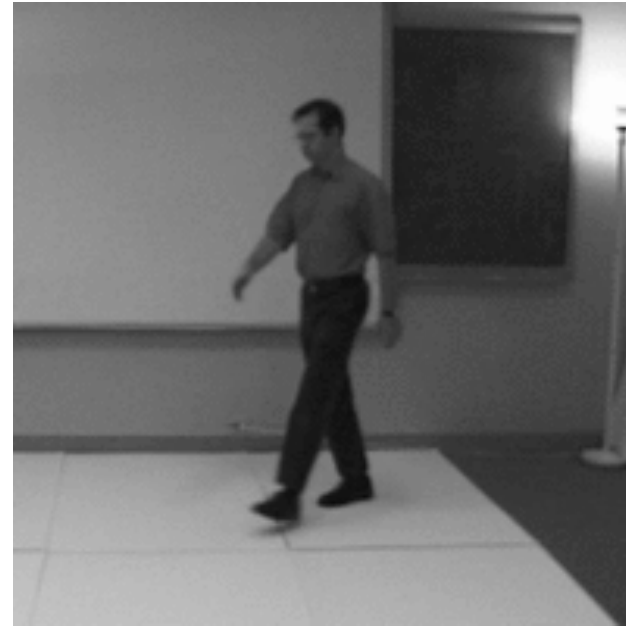
Global motion



Differential motion



Static background - Object moving

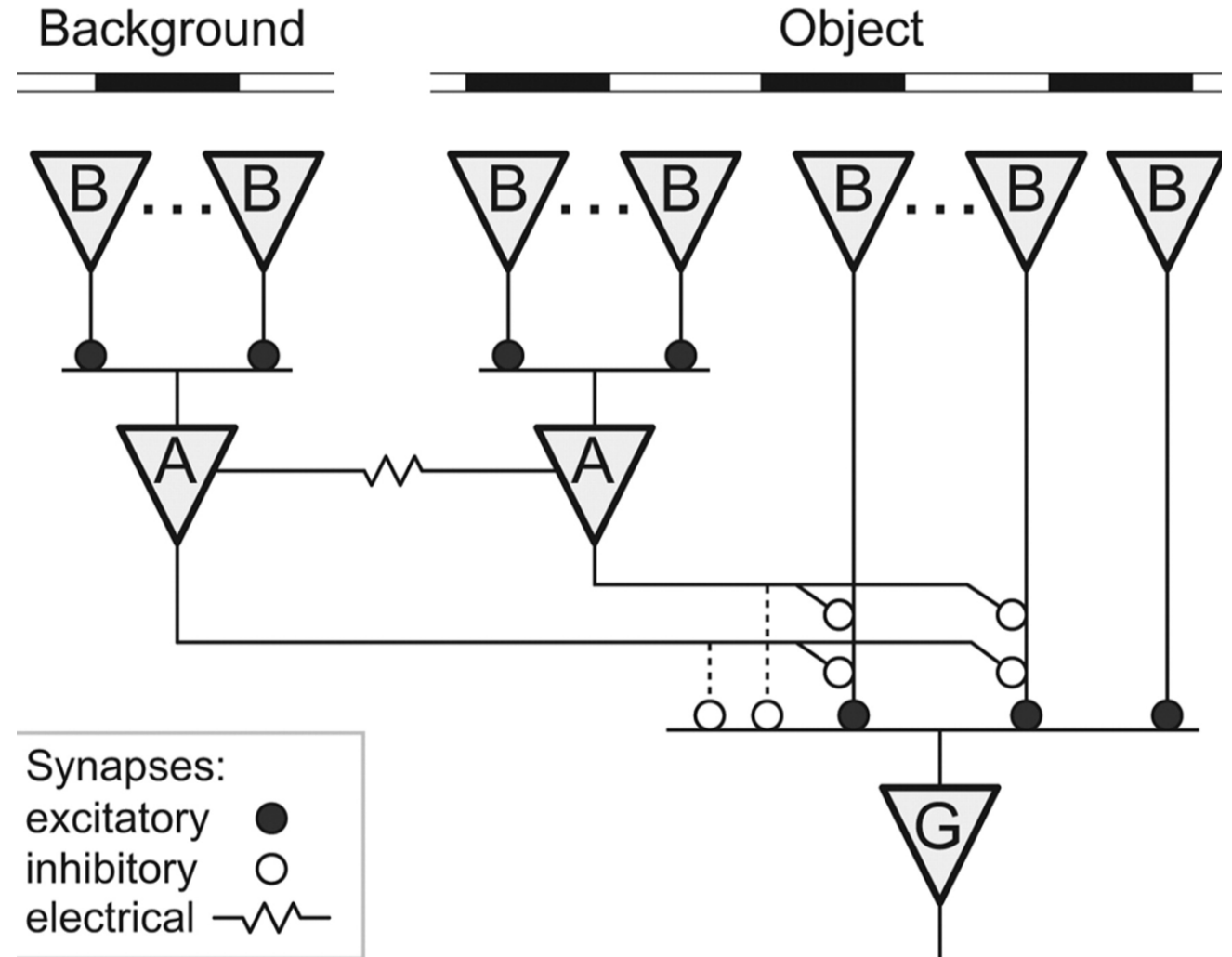


Background & Object moving

Retinal circuit related to motion

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

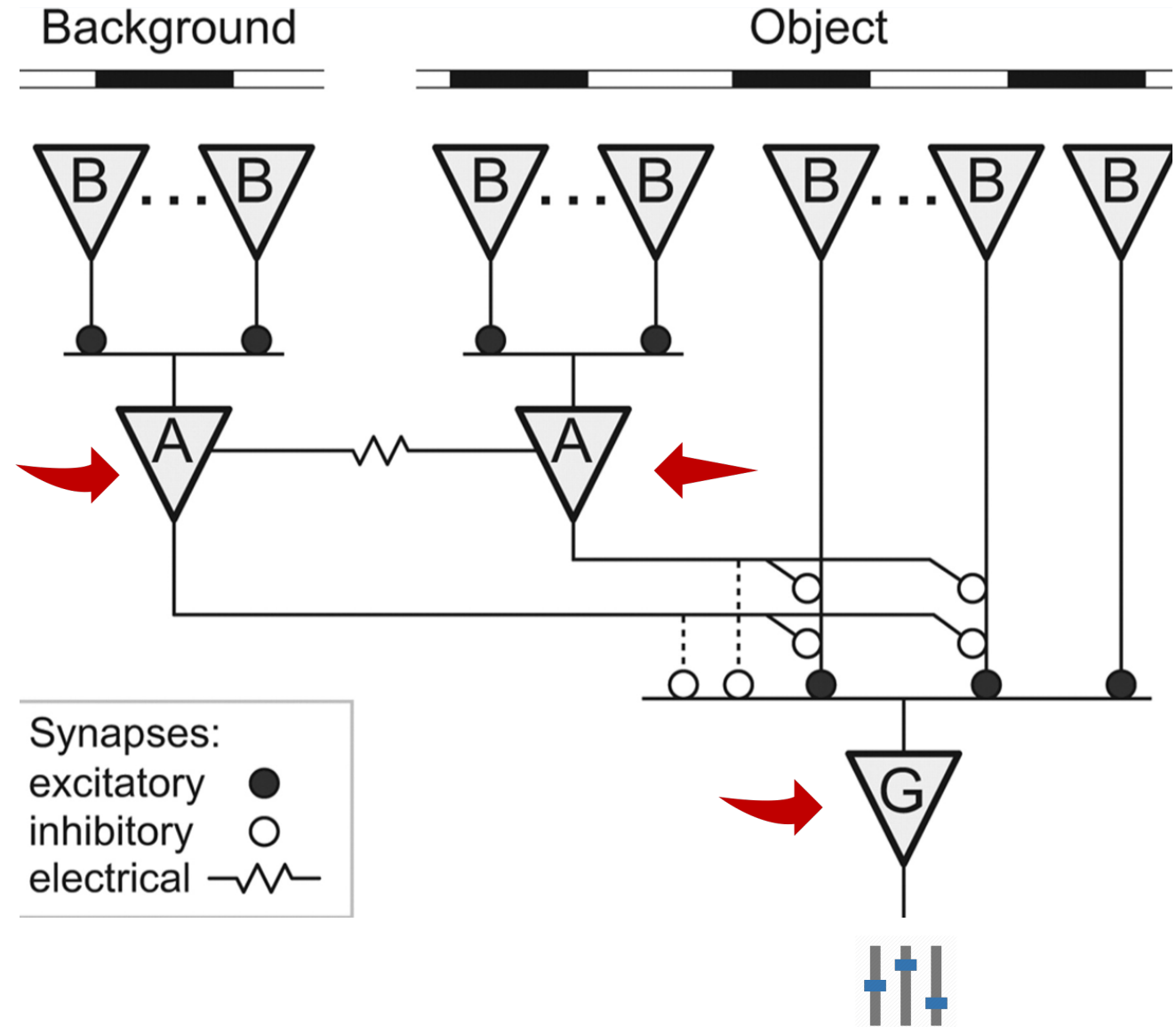
Background region: Inhibitory input to the ganglion cell (G) from amacrine cells (A).



CNO effect on the circuit

DREADDs on :

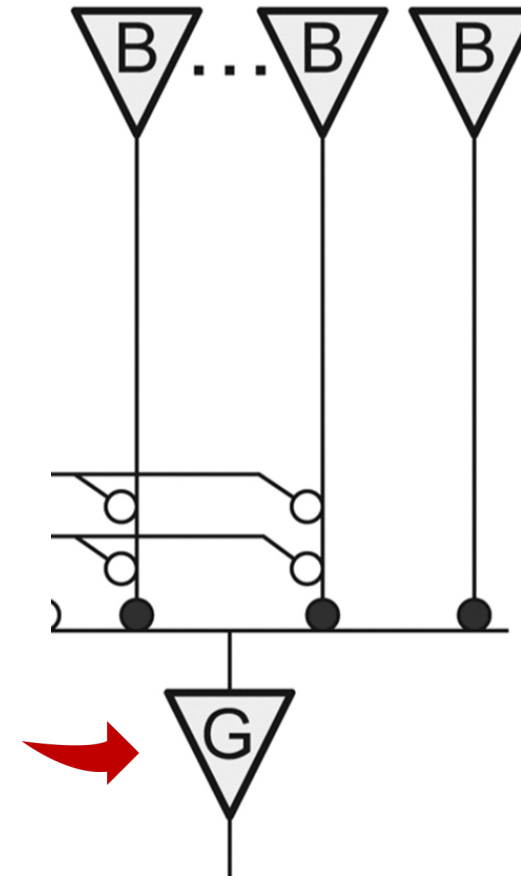
- Amacrine cells (ACs) and/or
- Ganglion cells (RGCs)



CNO effect on the circuit

DREADDs on Ganglion cells (RGCs)

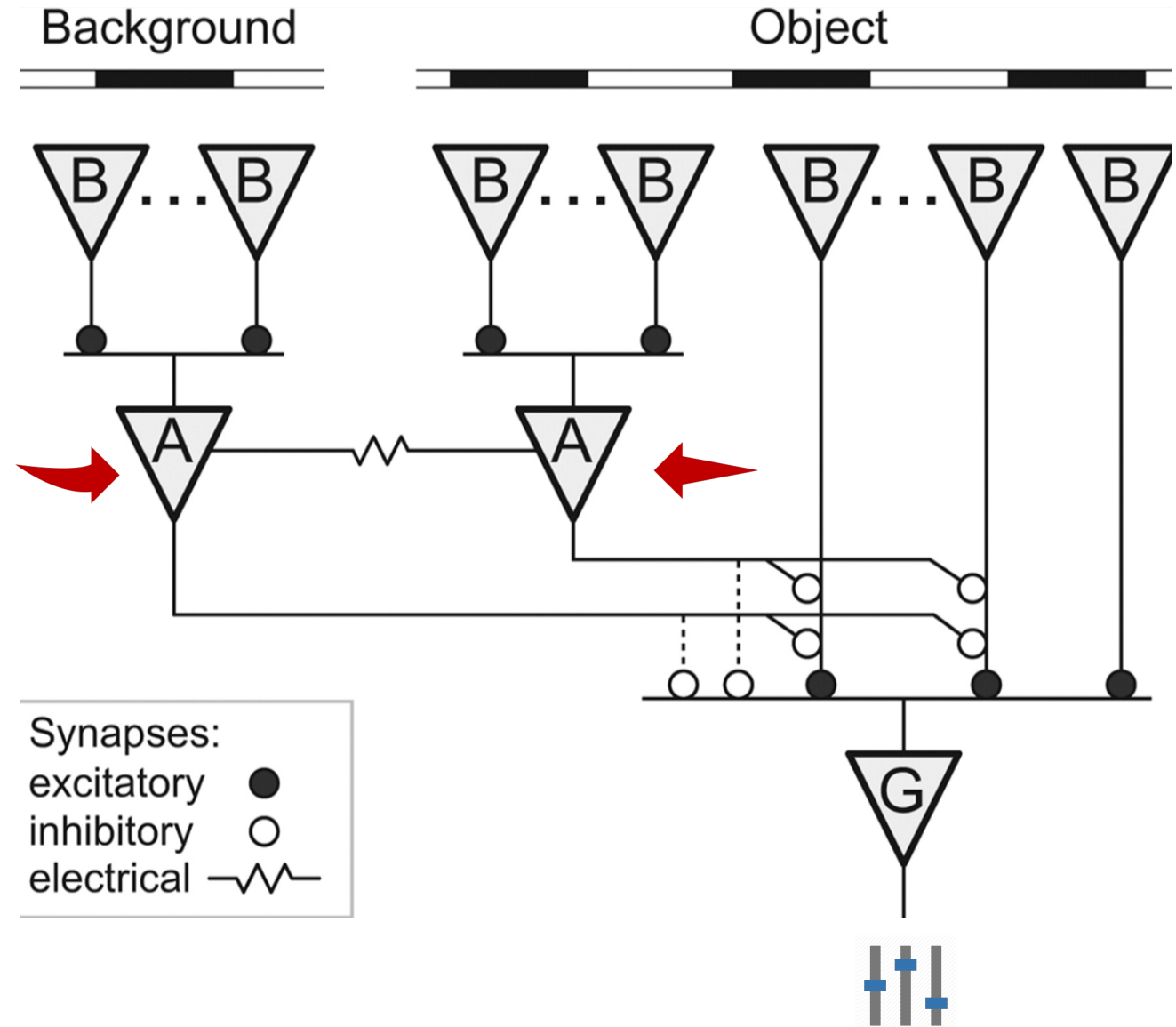
- If excitatory, the neuronal activity will increase
- If inhibitory, the neuronal activity will decrease



CNO effect on the circuit

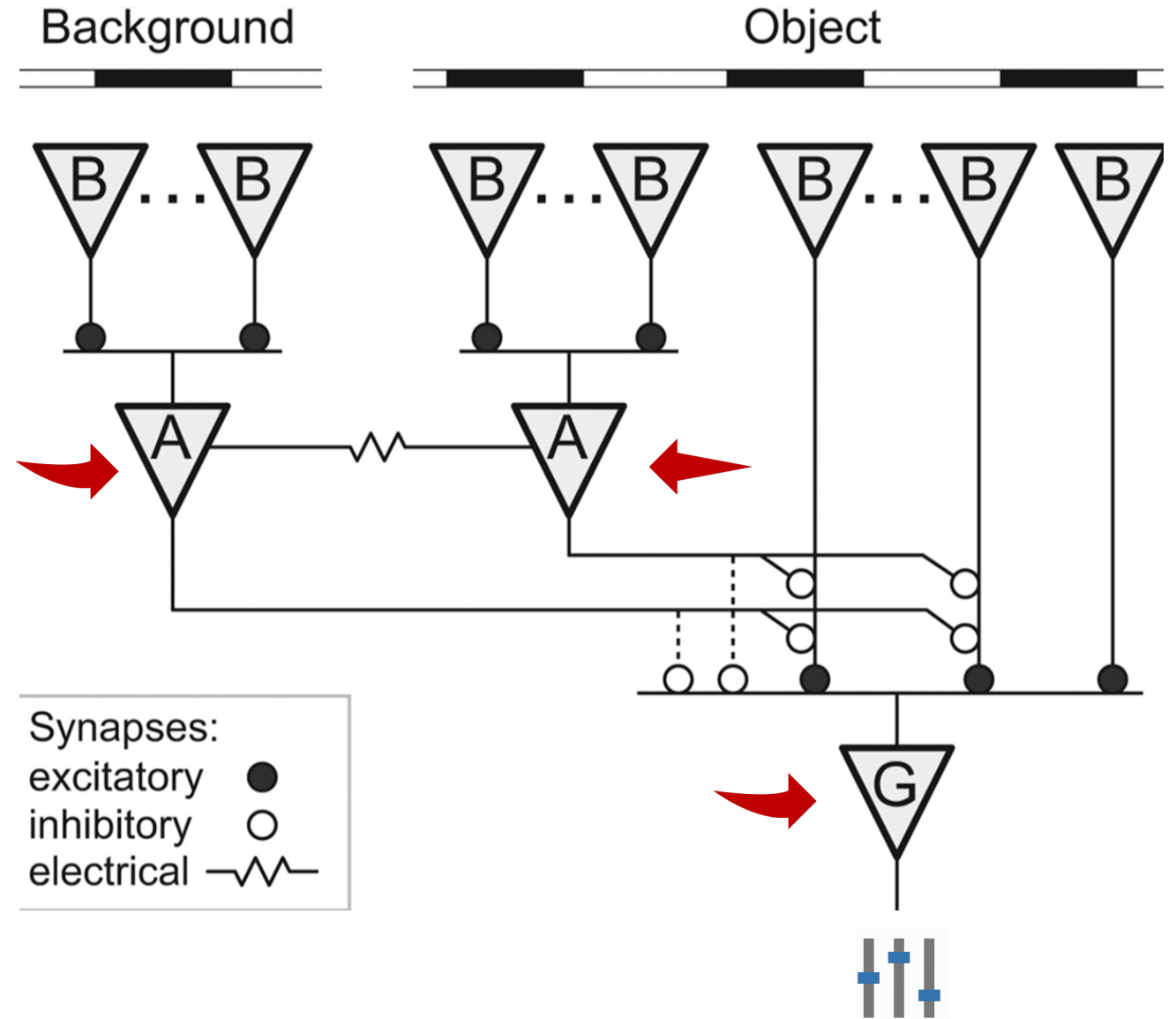
DREADDs on Amacrine cells (ACs):

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

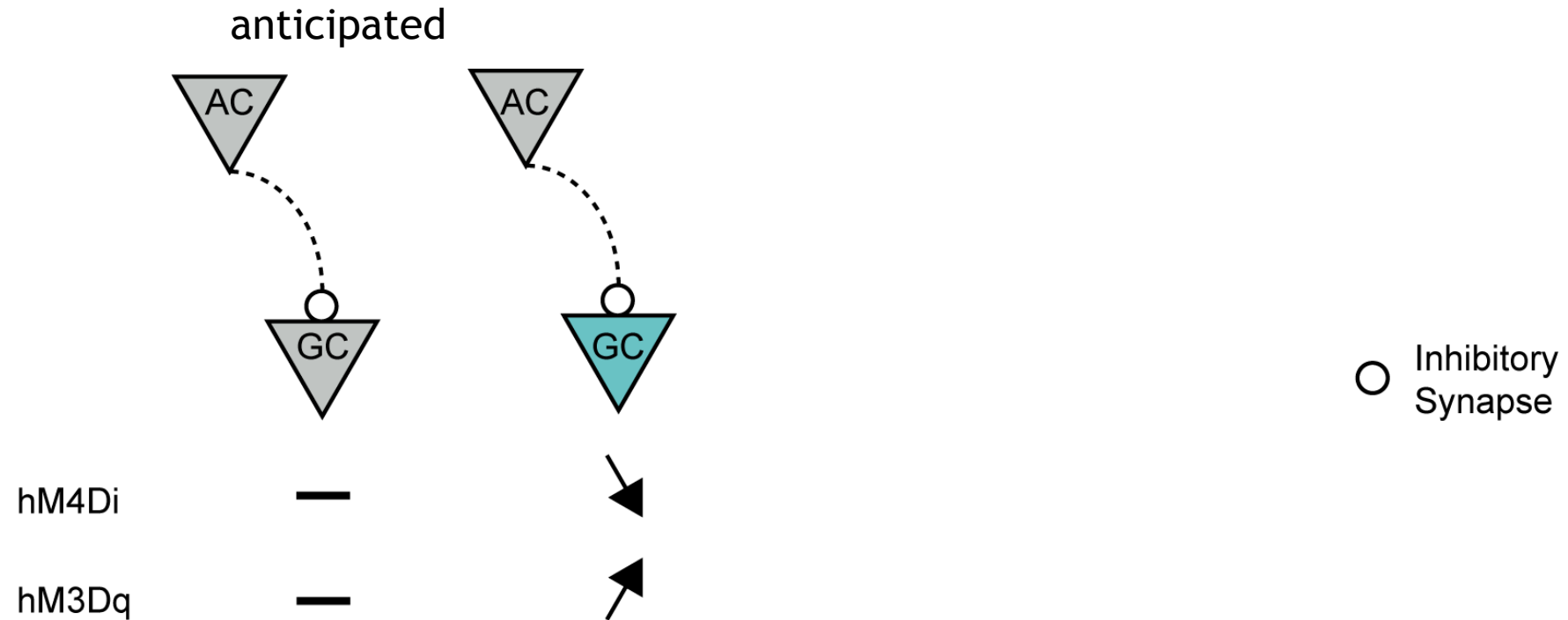


CNO effect on the circuit

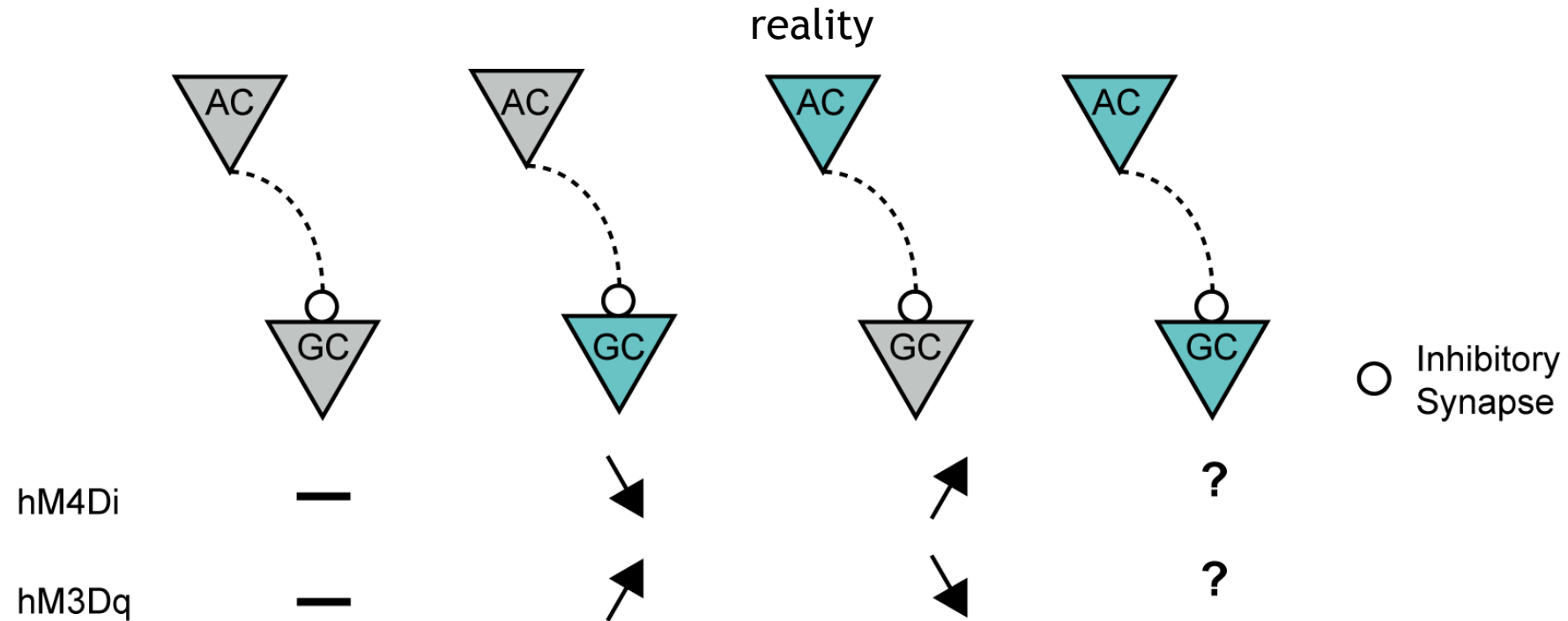
DREADDs on : ACs AND RGCs



Electrophysiological characterisation of Scnn1a and Grik4 DREADD RGCs

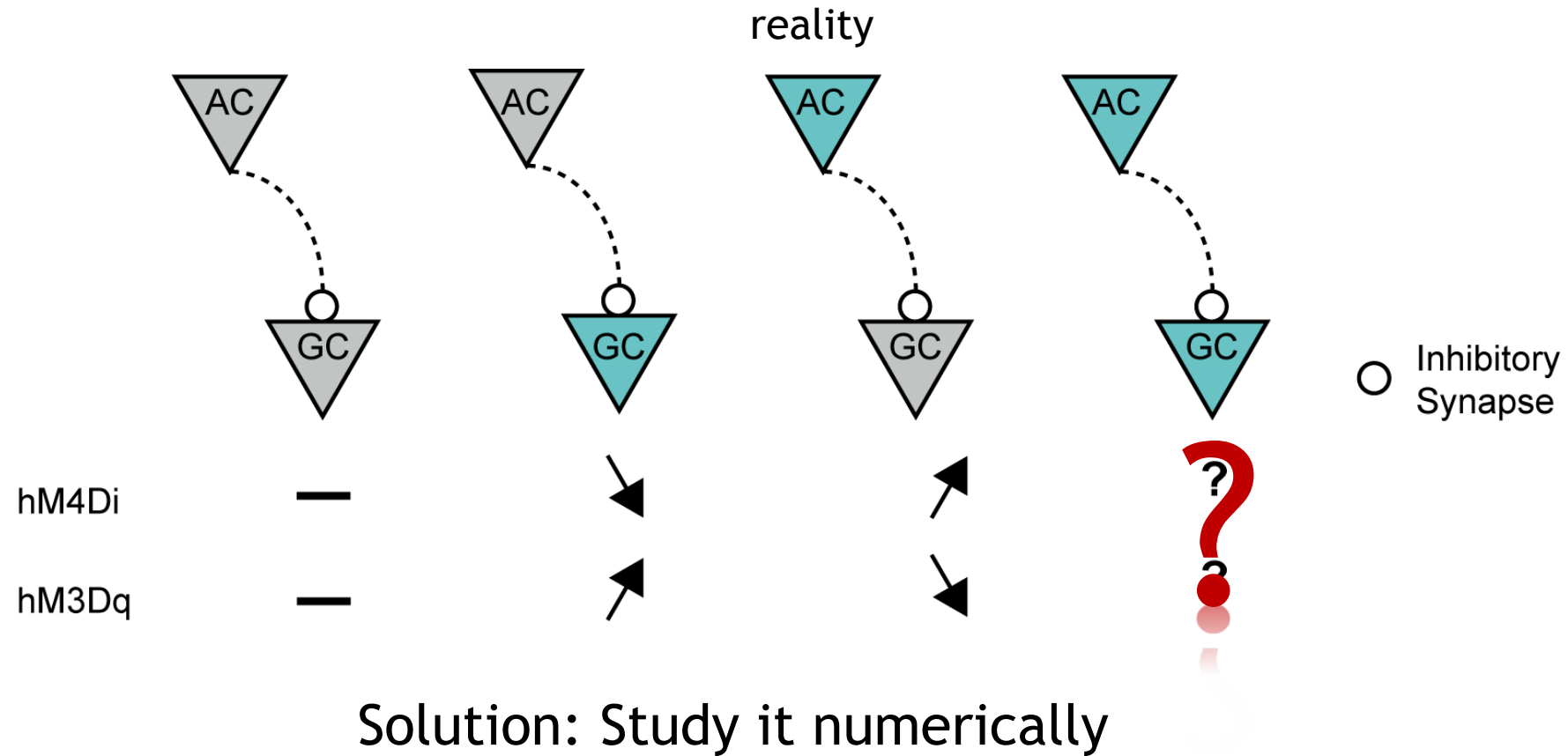


Electrophysiological characterisation of Scnn1a and Grik4 DREADD RGCs

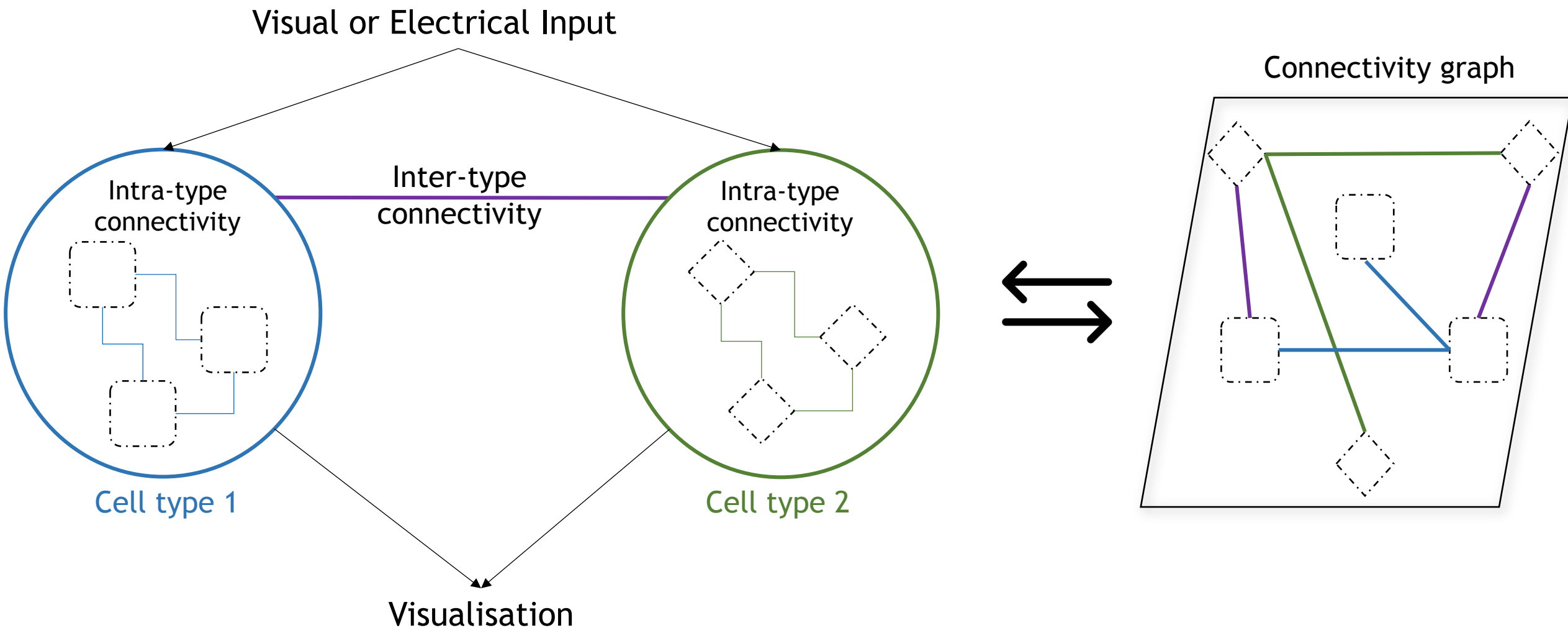


DREADDs in ACs makes the interpretation of functional results from DREADD-expressing RGCs more challenging.

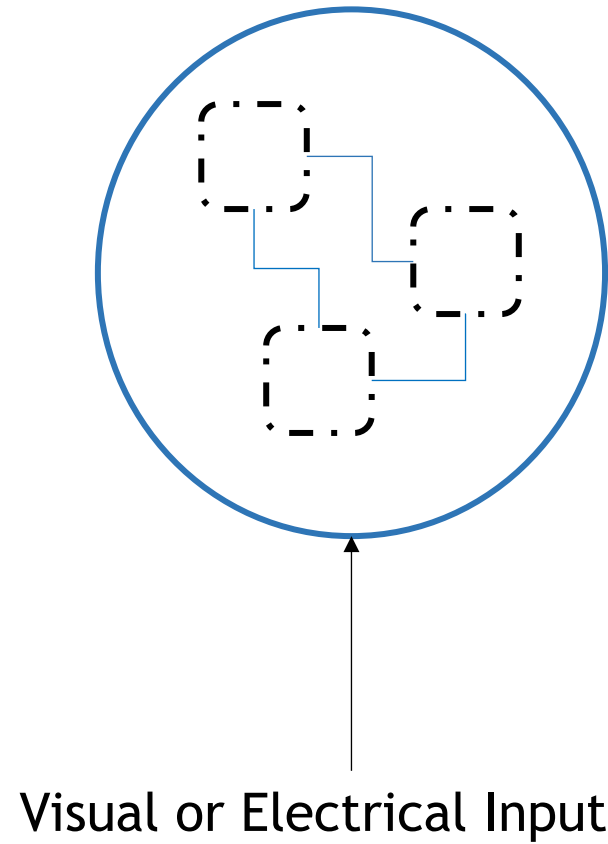
Electrophysiological characterisation of Scnn1a and Grik4 DREADD RGCs



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.

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

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 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

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

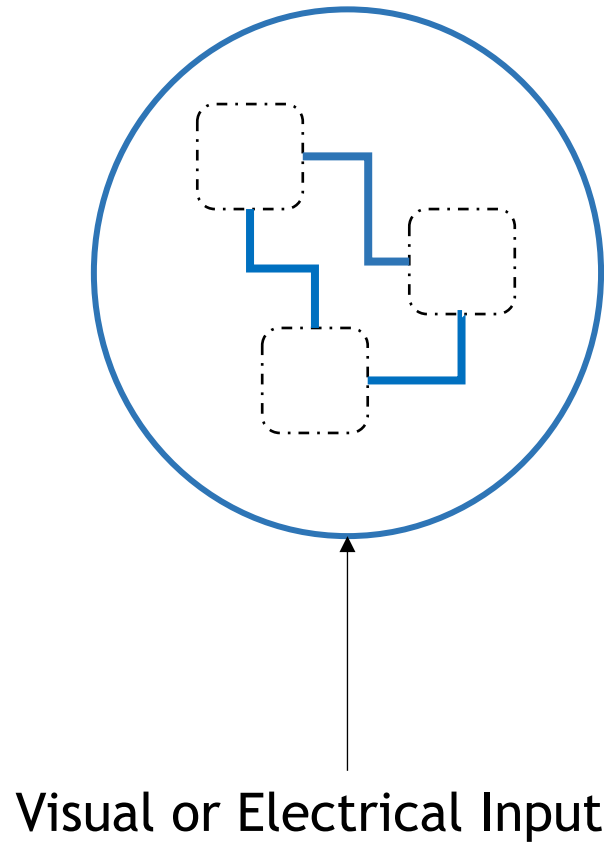
macularCell
+ State X : vector + Parameters μ : vector + Isyn : double + Iext : double
+ function $f (X, \mu, Isyn, Iext) : void$

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- ✓ A function controlling the cell's evolution
- ✓ **Isyn** : A synaptic input corresponding to synaptic connections with other cells
- ✓ **lext** : 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 + lext : double
+ function $f (X, \mu, Isyn, lext) : void$

Basic building blocks - synapse



Synapse

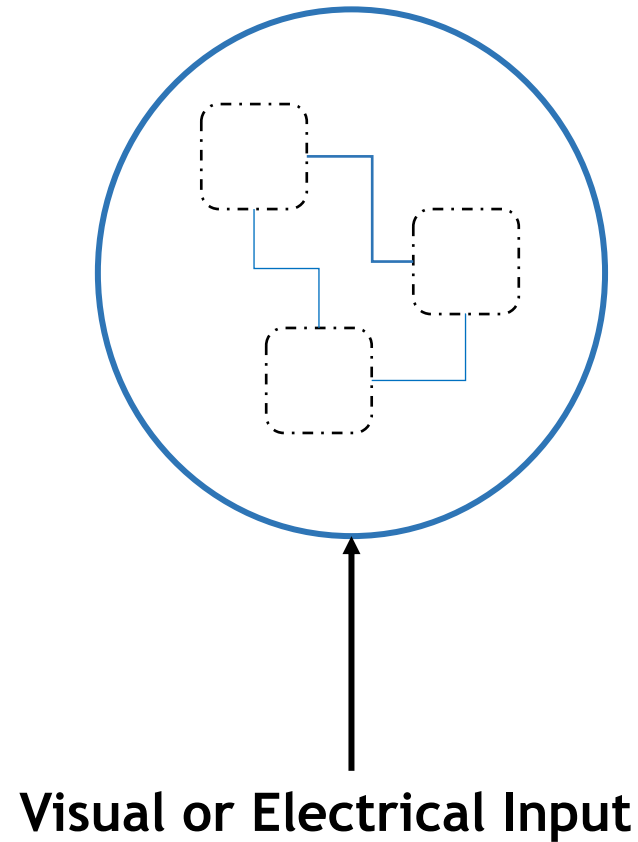
macularSynapse

+ 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



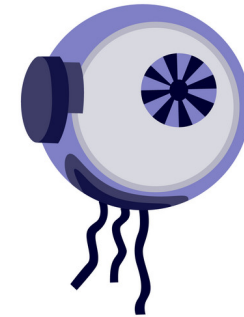
Visual Input



Virtual Retina module

- ✓ Emulate the outer plexiform layer (OPL) current

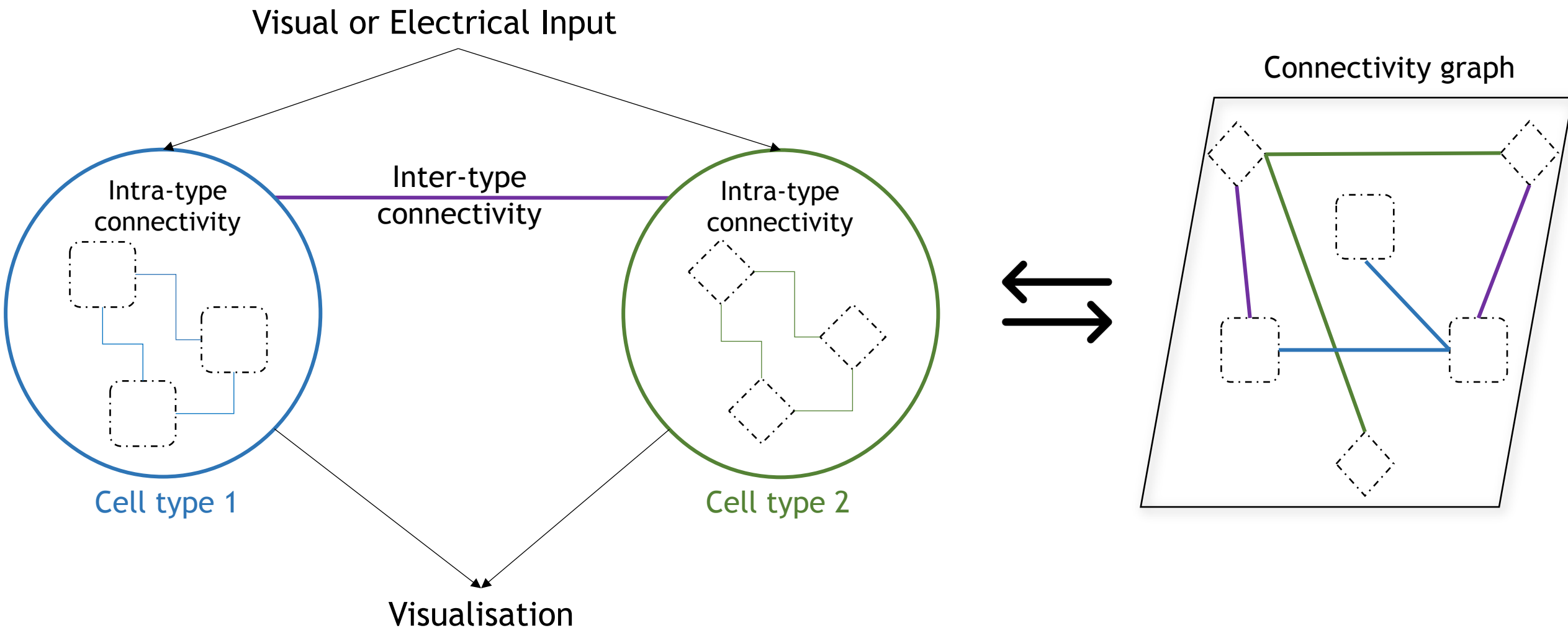
A.Wohrer et al., 2009



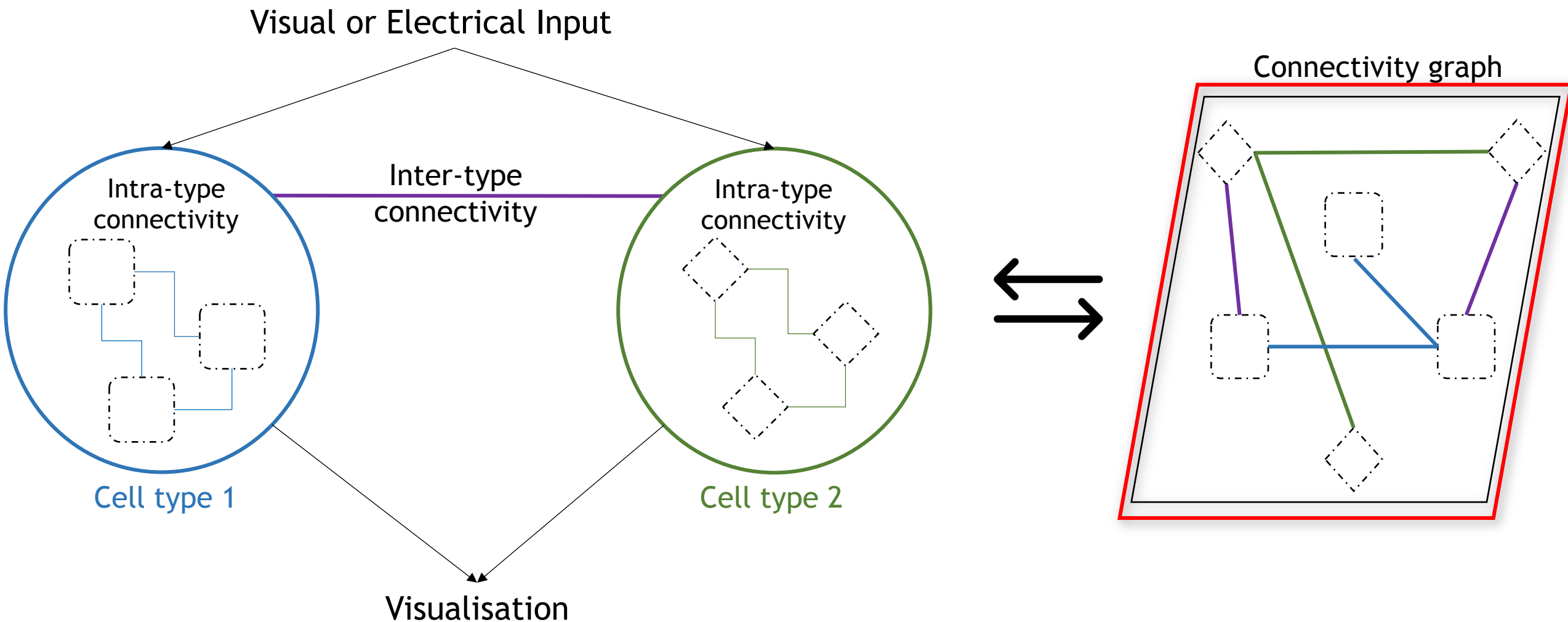
Retinal prosthesis

- ✓ Emulate the electric current provided by an electrode

General structure



General structure



Graph

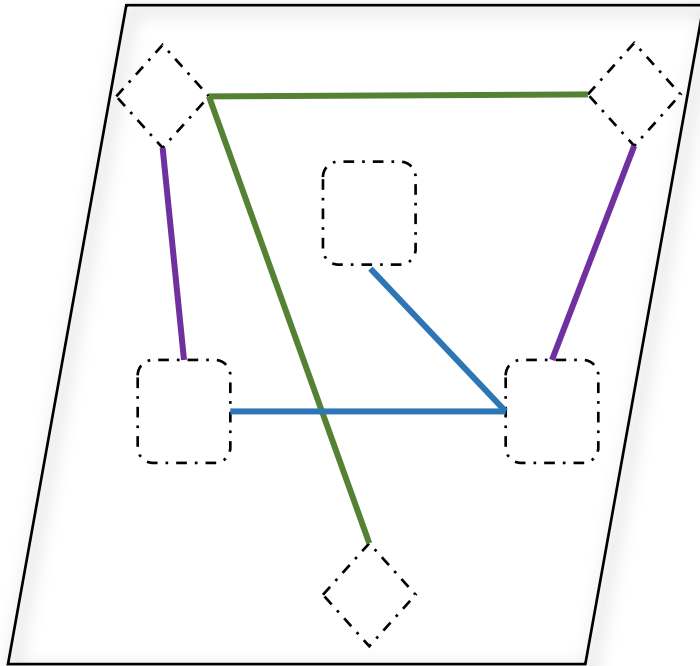
macularGraph

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

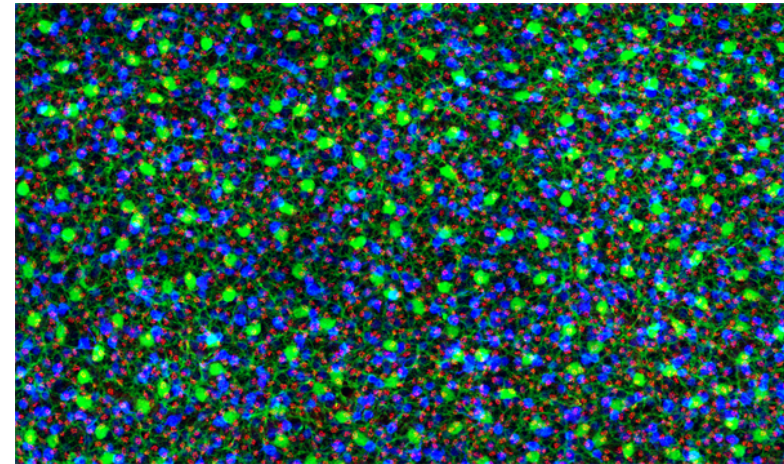
- ✓ Cell types
- ✓ Synapse types
- ✓ Cell coordinates
- ✓ Synapse indices

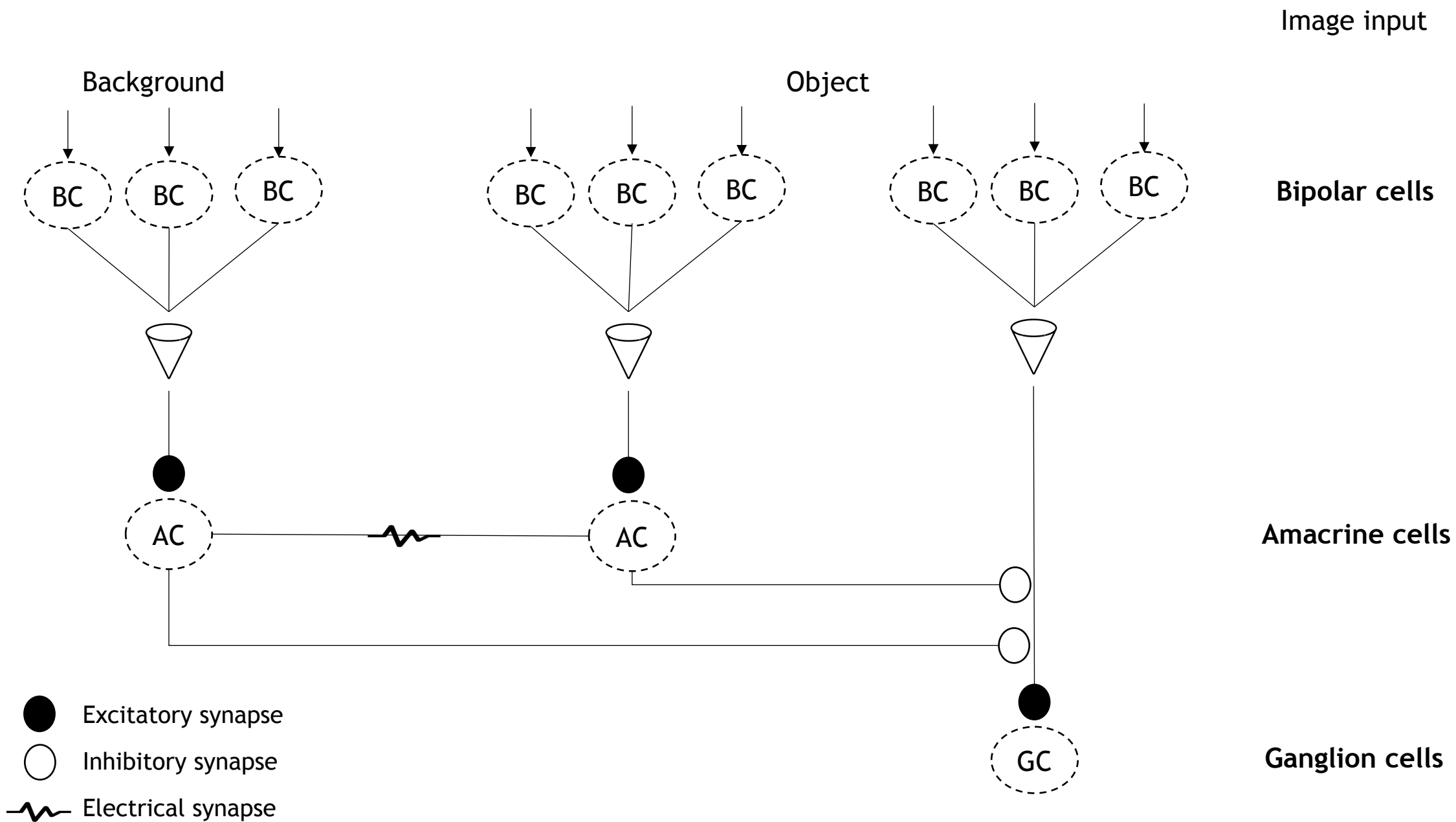
Graph

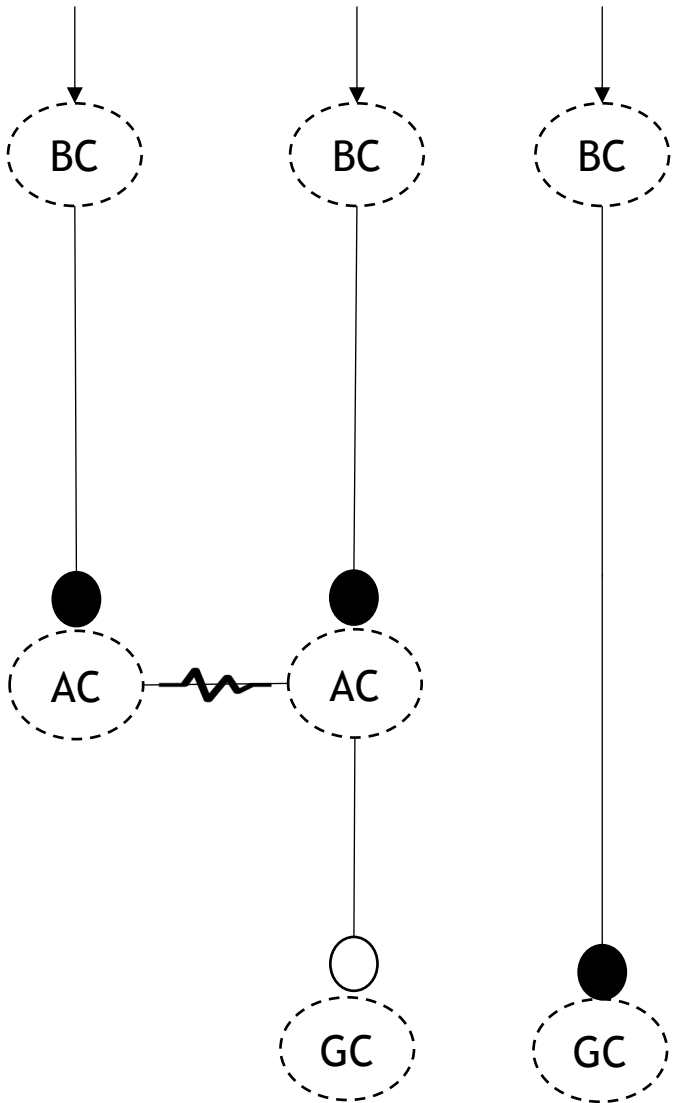
Connectivity graph

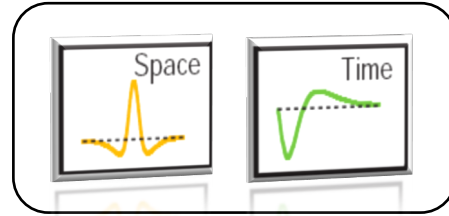
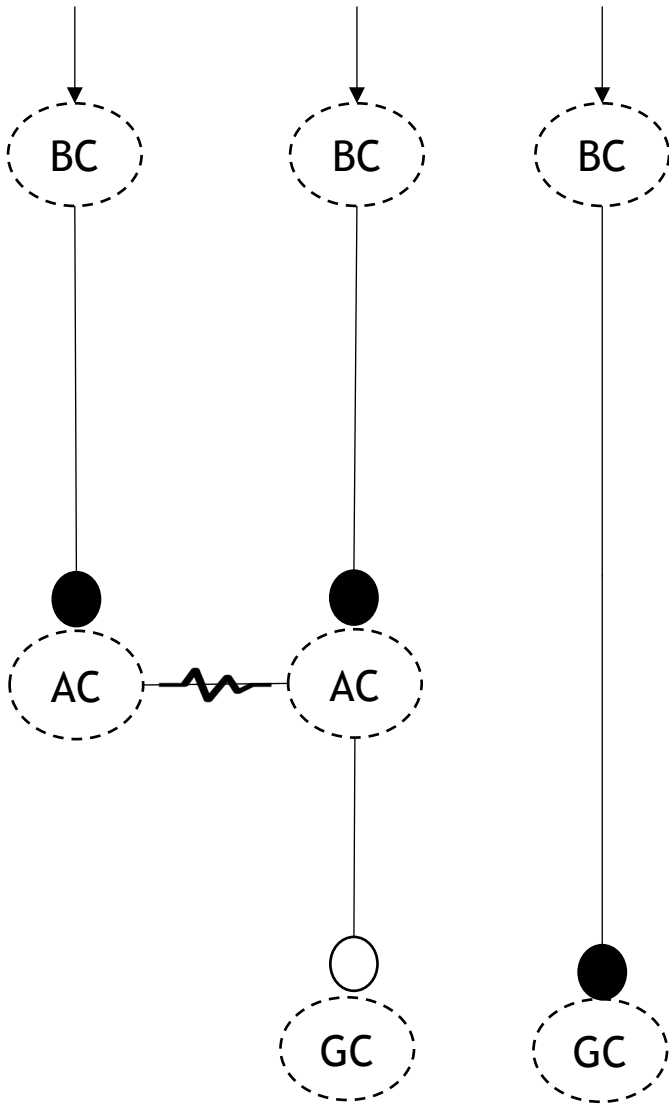


- ➡ Design a local circuit with specific connectivity patterns
- ➡ Deploy it to the whole retina



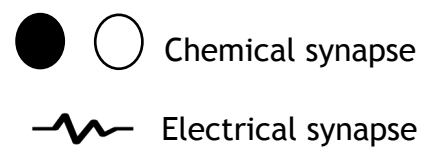
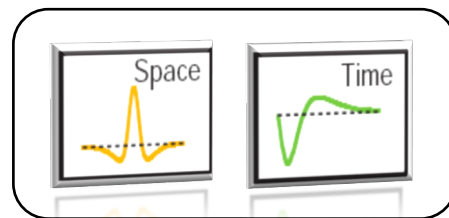
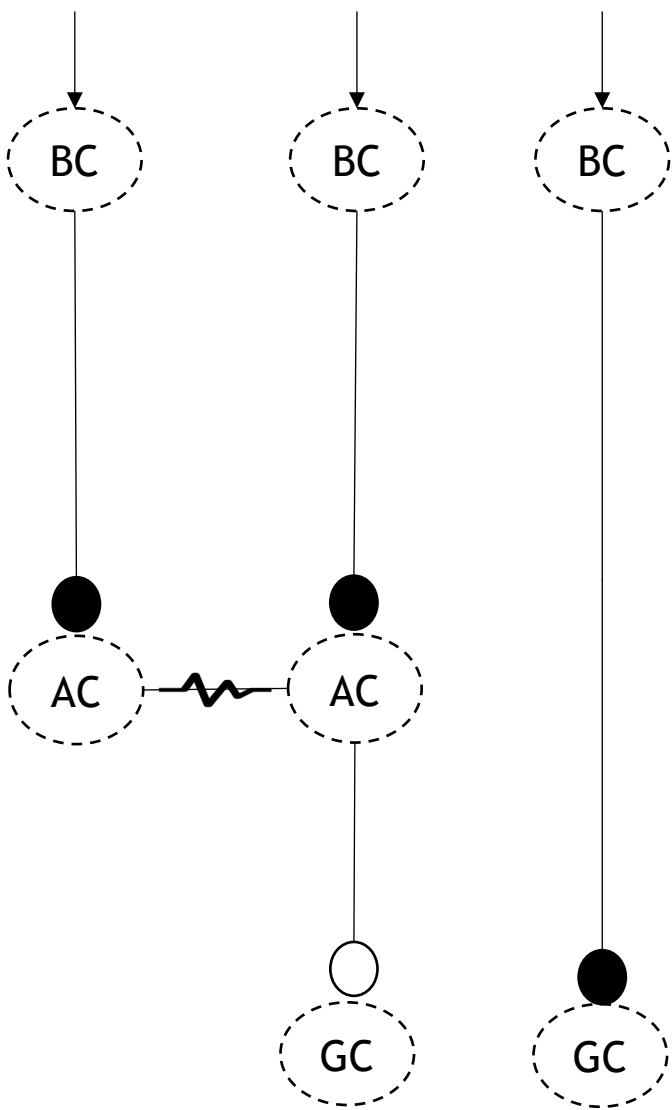






$$K(x, y, t) = K_S(x, y)K_T(t)$$

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

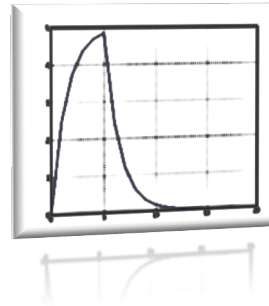
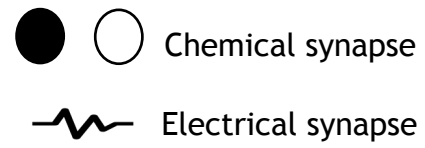
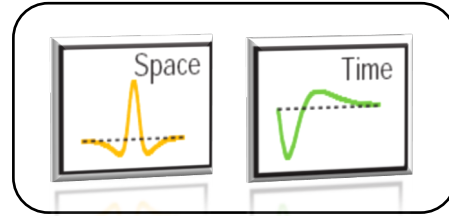
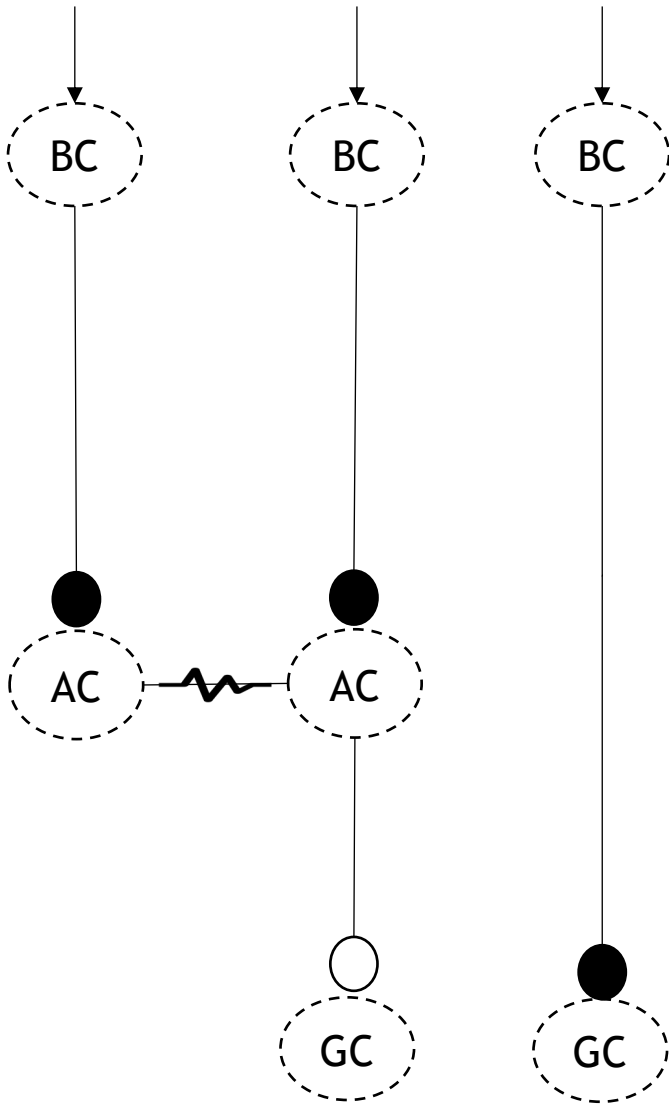


$$K(x, y, t) = K_S(x, y)K_T(t)$$

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

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

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



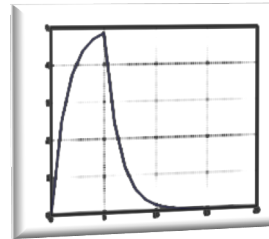
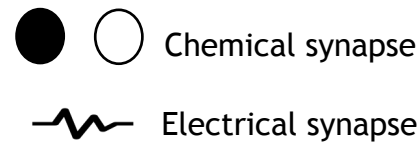
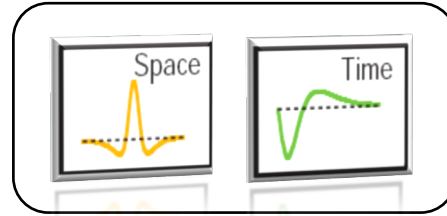
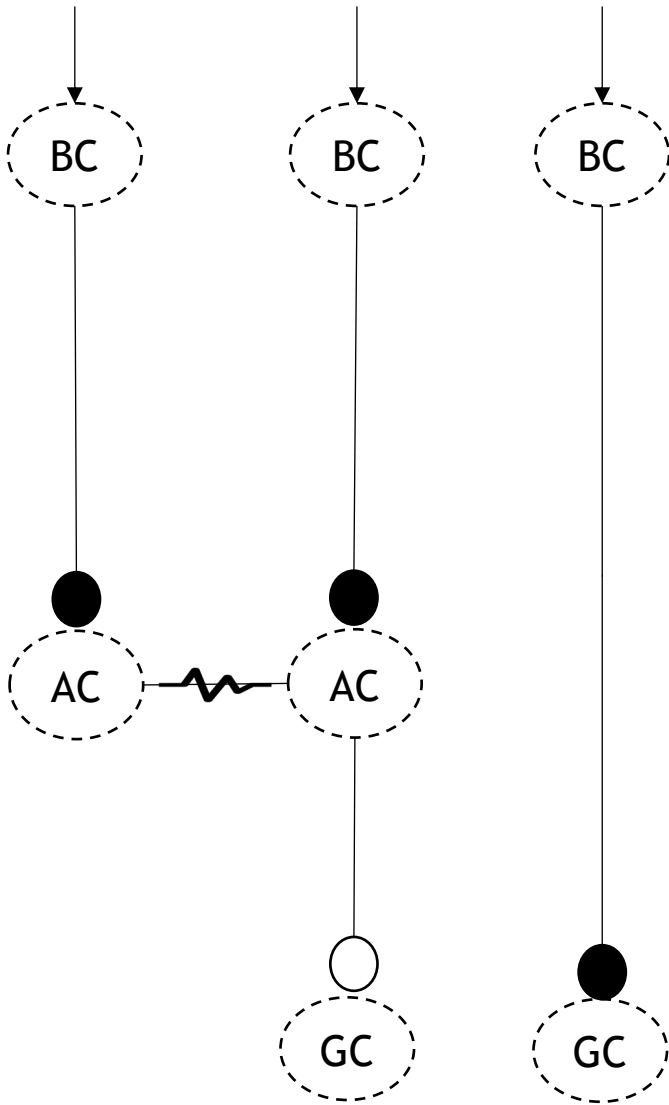
$$K(x, y, t) = K_S(x, y)K_T(t)$$

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

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

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

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



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

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

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

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

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

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













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

48

macular



Ganglions

Video

>

↔

I

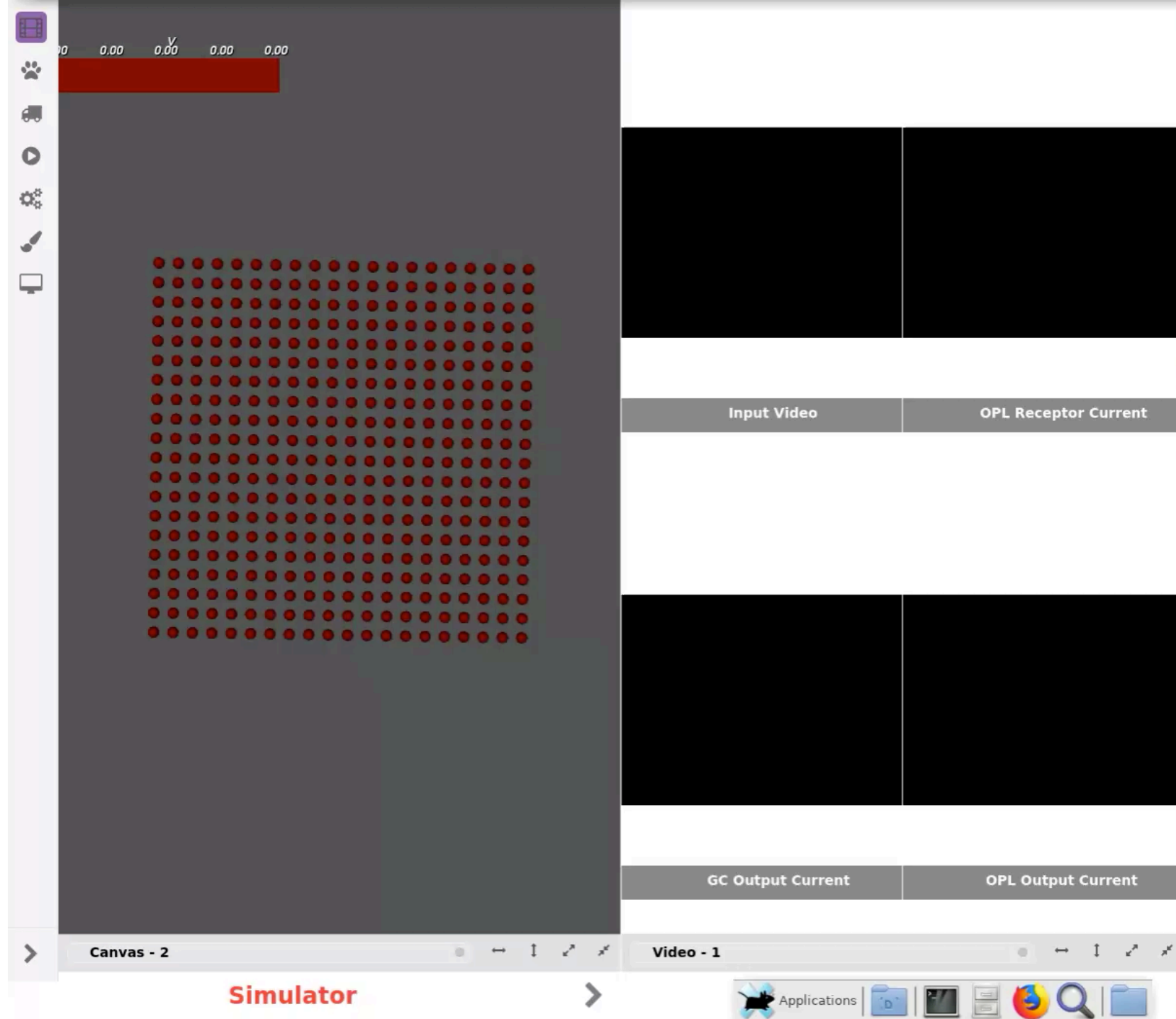
↗

↘

Simulator

>

Graph Generator



The background features a black and white hexagonal pattern. Overlaid on this are several clusters of bright green particles. One large cluster in the lower-left shows a central bright point with many fine lines radiating outwards, resembling a star or a complex network. Other smaller, more diffuse clusters of green dots are scattered in the upper-left and upper-right areas.

Thank you!

Questions?