Ion channels and properties of large neuronal networks: a computational study of re.nal waves during development

D Karvouniari, Lionel Gil, Olivier Marre, Serge Picaud, Bruno Cessac

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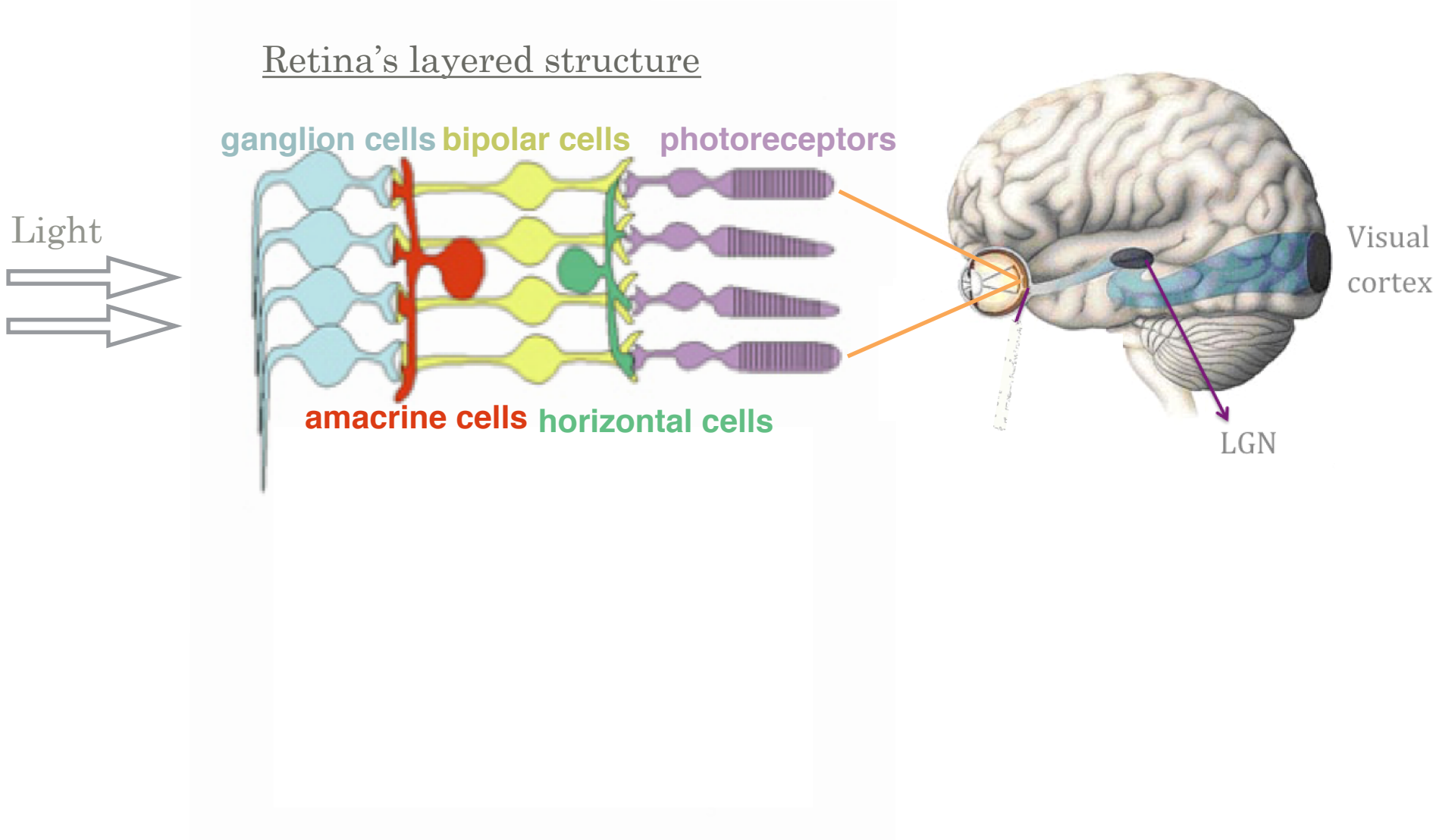
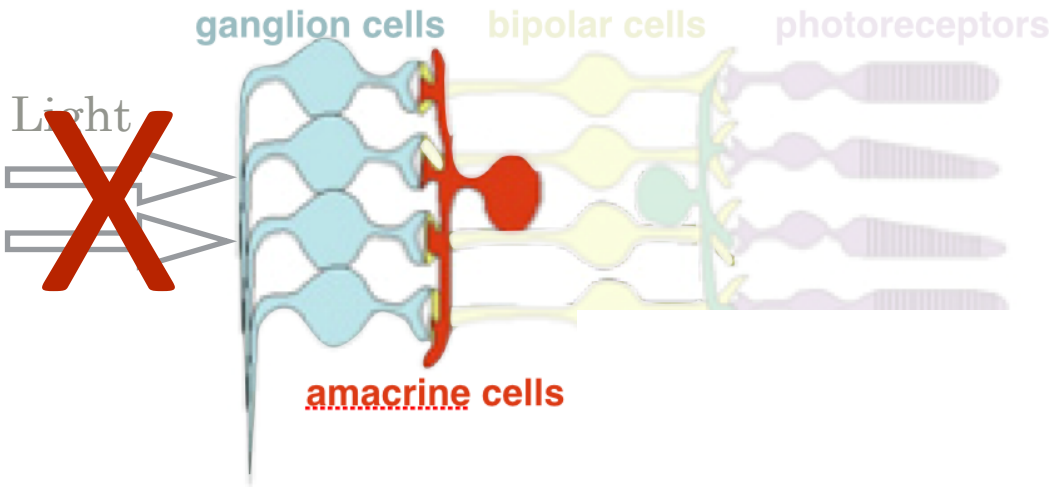
The structure of the adult retina



The structure of the retina during development

Retina's layered structure
is shaped during development

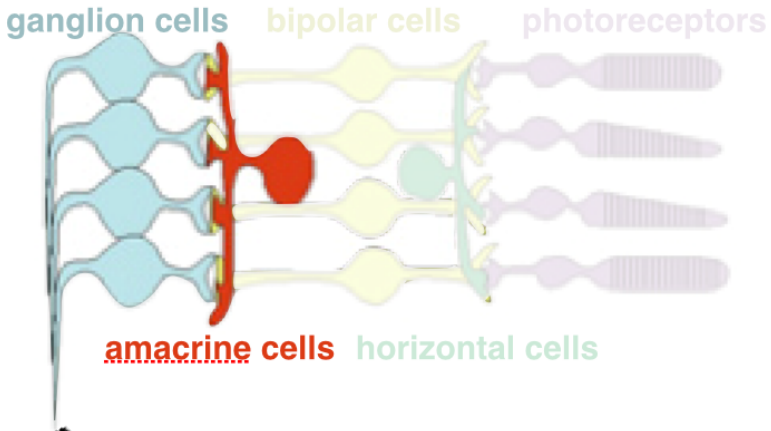


But How? ⇒ **Retinal waves!**

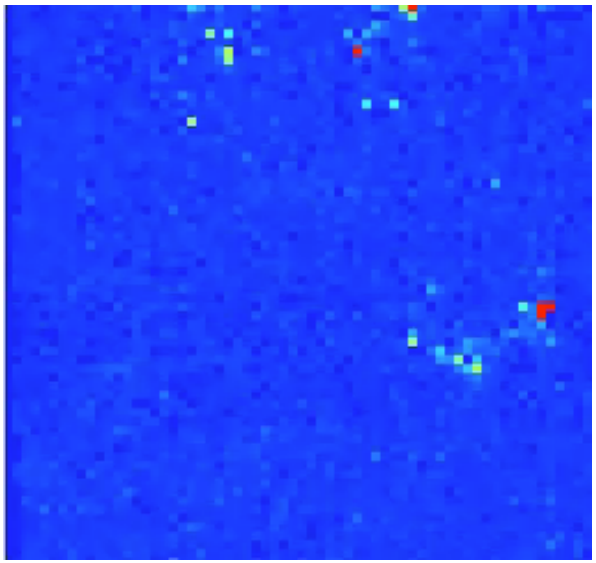
Retinal waves

Spontaneous spatio-temporal waves during development
Disappear short after birth when vision is functional

Recordings from the retina



Multi-electrode array (MEA)



(Maccione et al. 2014)

MEA recording of the voltage from a P11 mouse retina in the presence of 10 μM bicuculline.

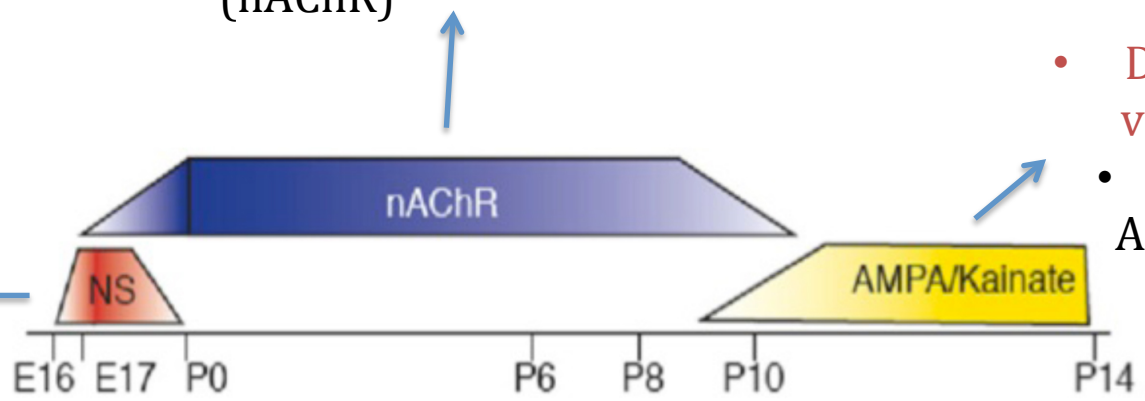
Stages of Retinal Waves During Development

Stage II

- Retinotopic mapping
- Nicotinic Acetylcholine Receptors (nAChR)

Stage III

- Disappear when vision is functional
- Glutamate – AMPA receptors



Stage I

- Formation of retina circuitry
- Chemical synapses <u>not</u> formed yet
- Gap juction-mediated

Stages of Retinal Waves During Development

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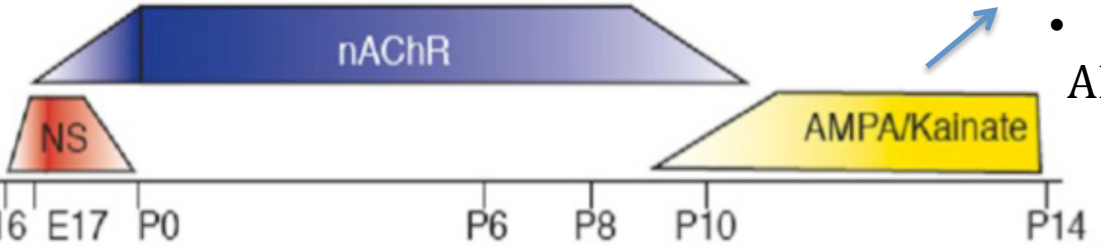

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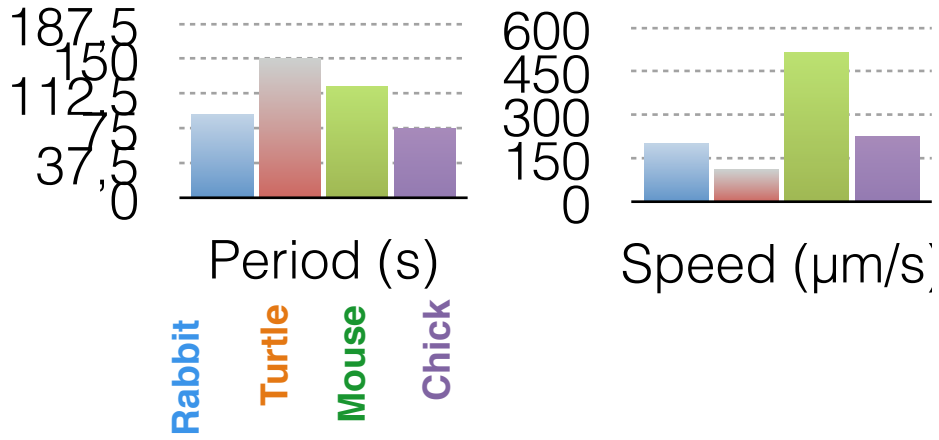
Variability within retinal waves

i) Across species

Godfrey et al. 2007



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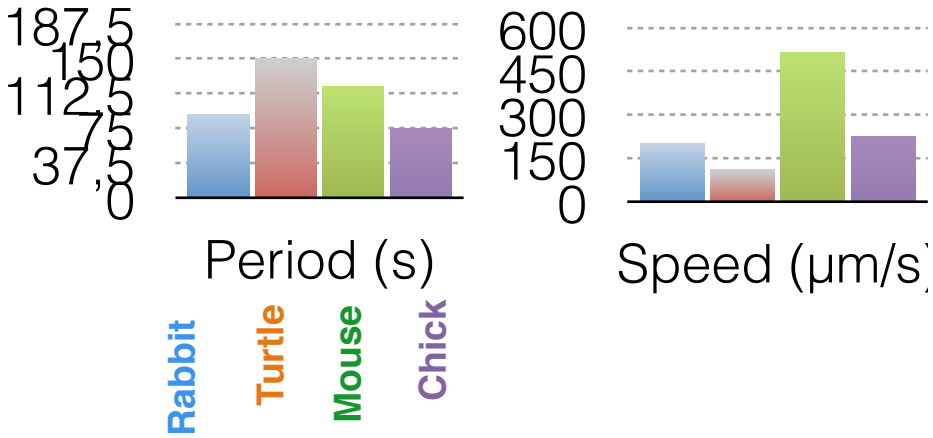
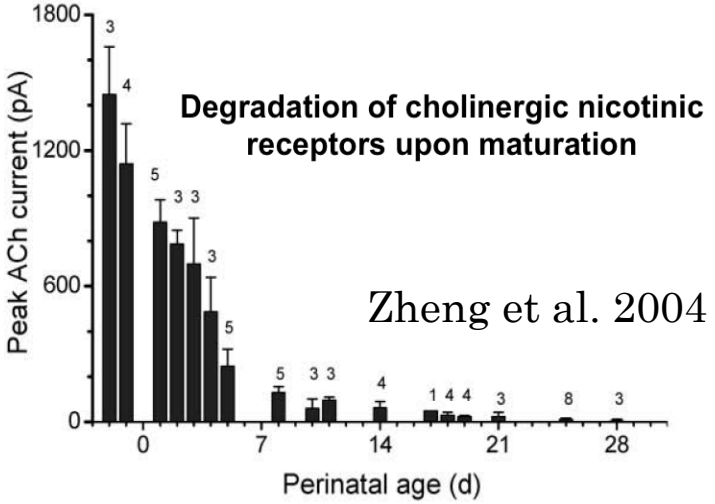


ii) Development



Zheng et al. 2004

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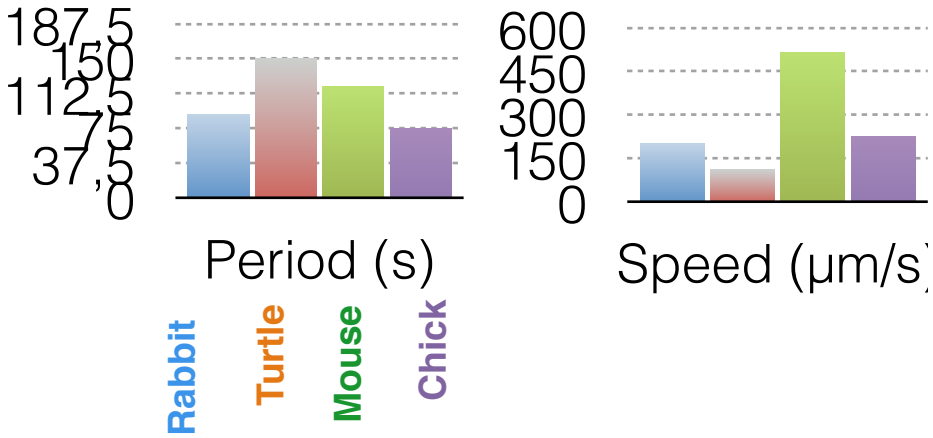

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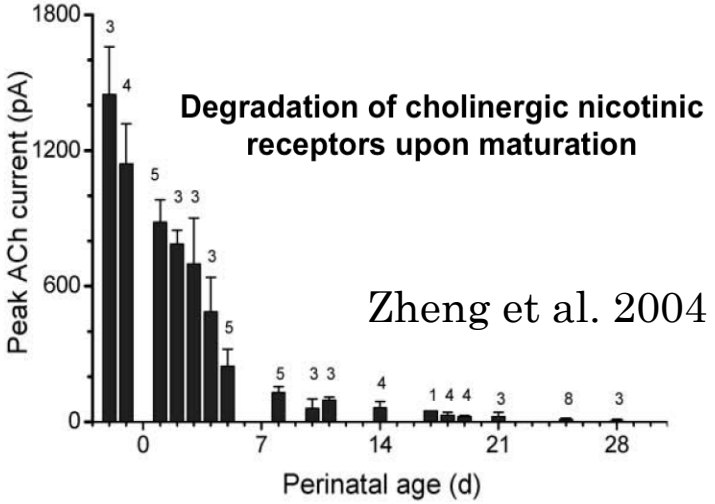
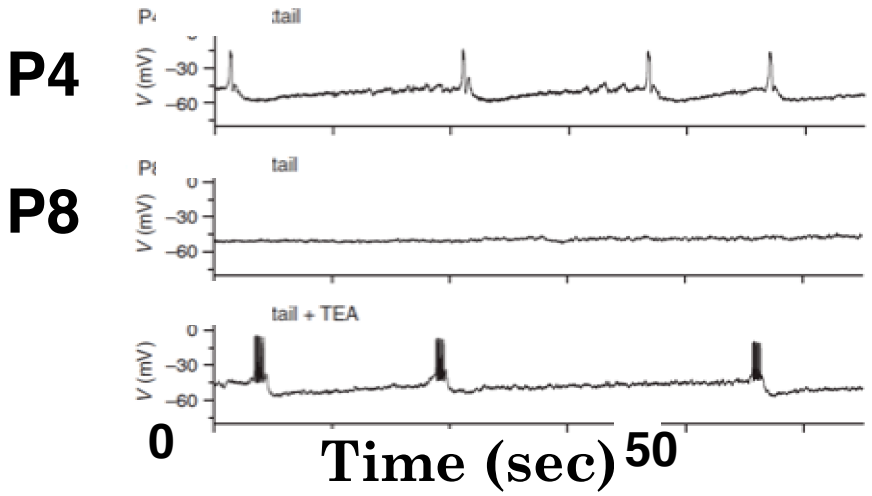


iii) Pharmacology



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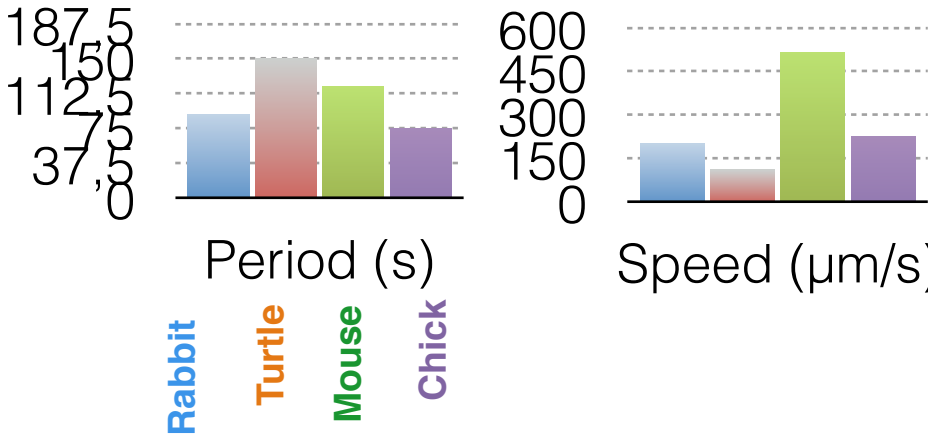

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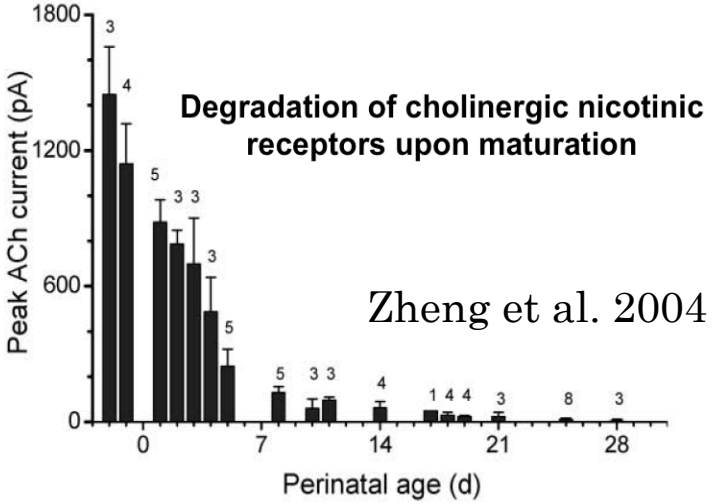

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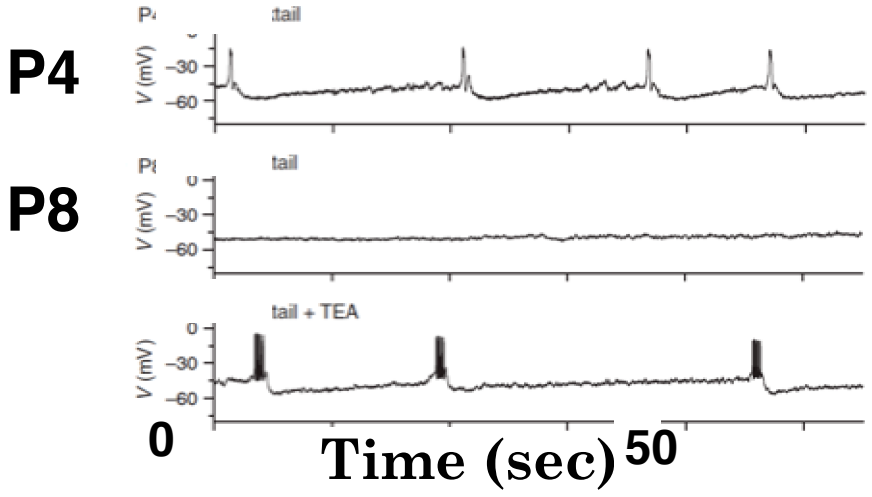
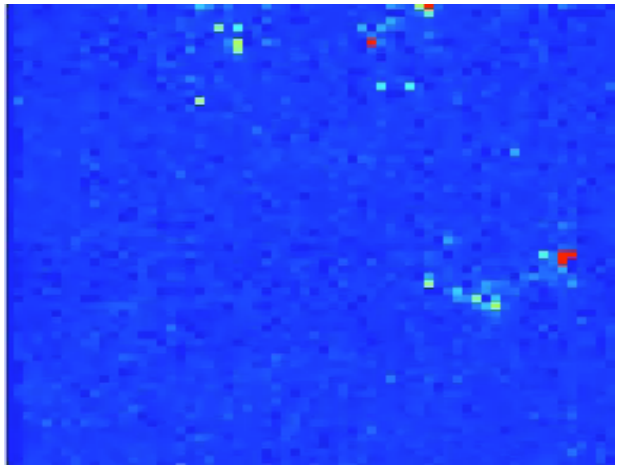


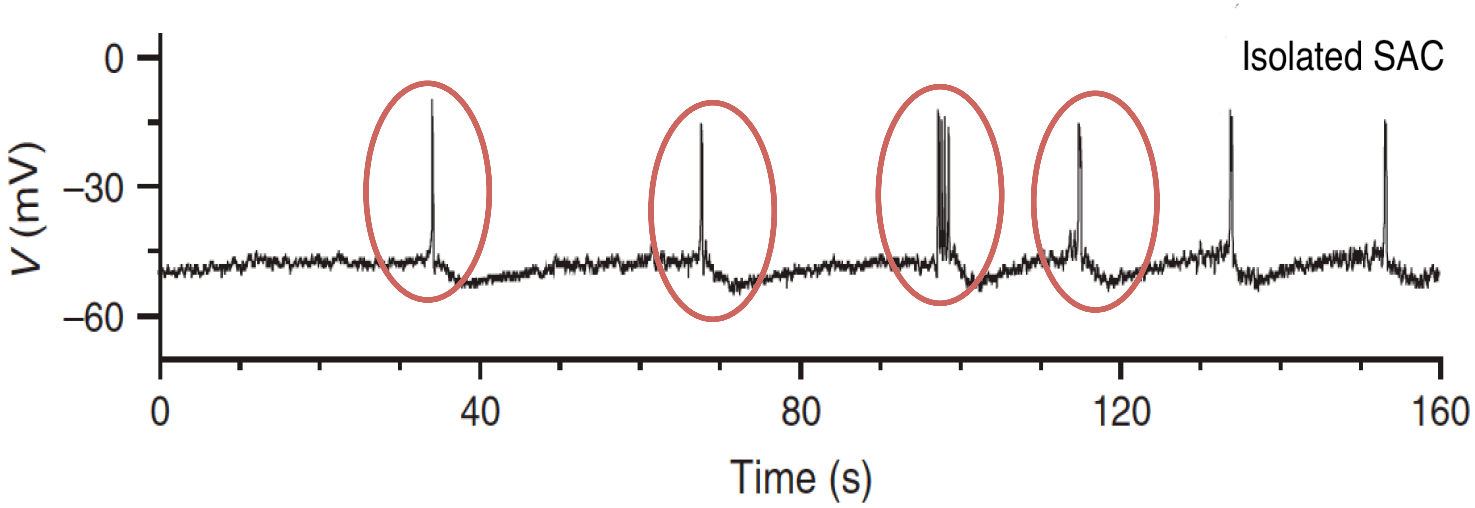
iv) Spatial Variability



Experiments for the emergence of retinal waves

Retinal waves require three components:

i) Spontaneous bursting activity



Experiment for isolated neurons,
Zheng et al., 2006, Nature

Experiments for the emergence of retinal waves

Retinal waves require three components:

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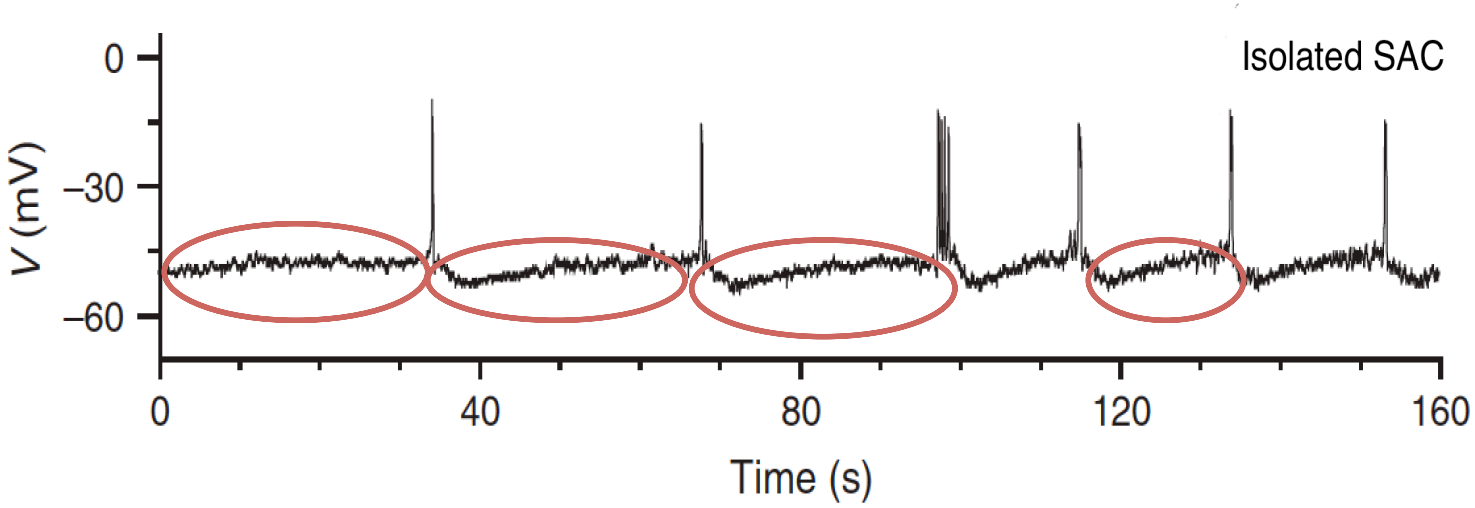
ii) Refractory mechanism (slow After HyperPolarisation- sAHP)



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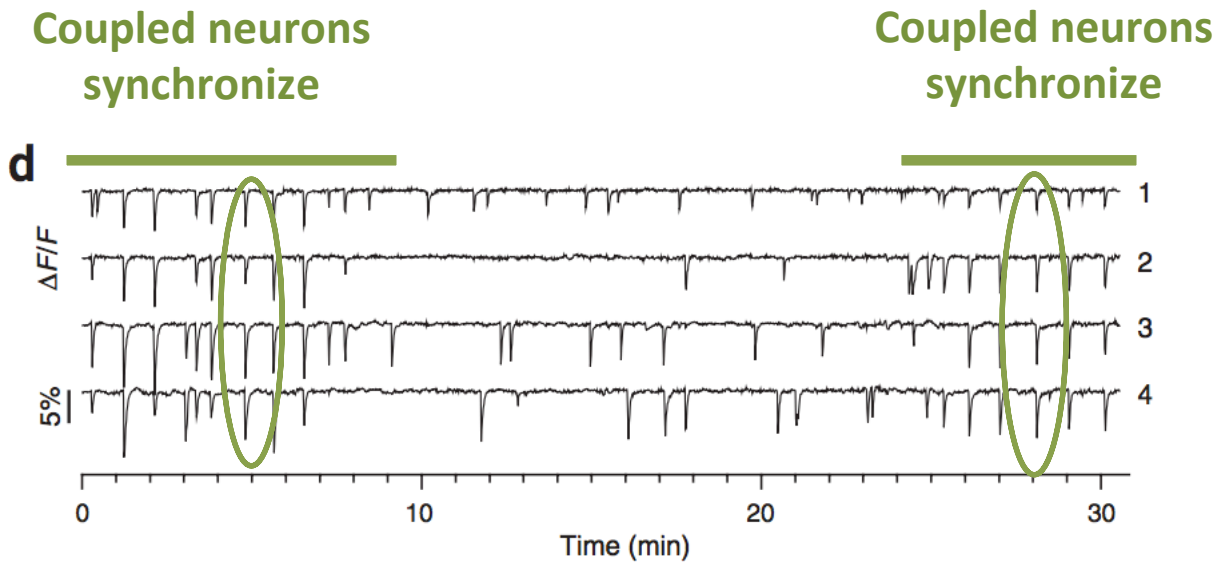

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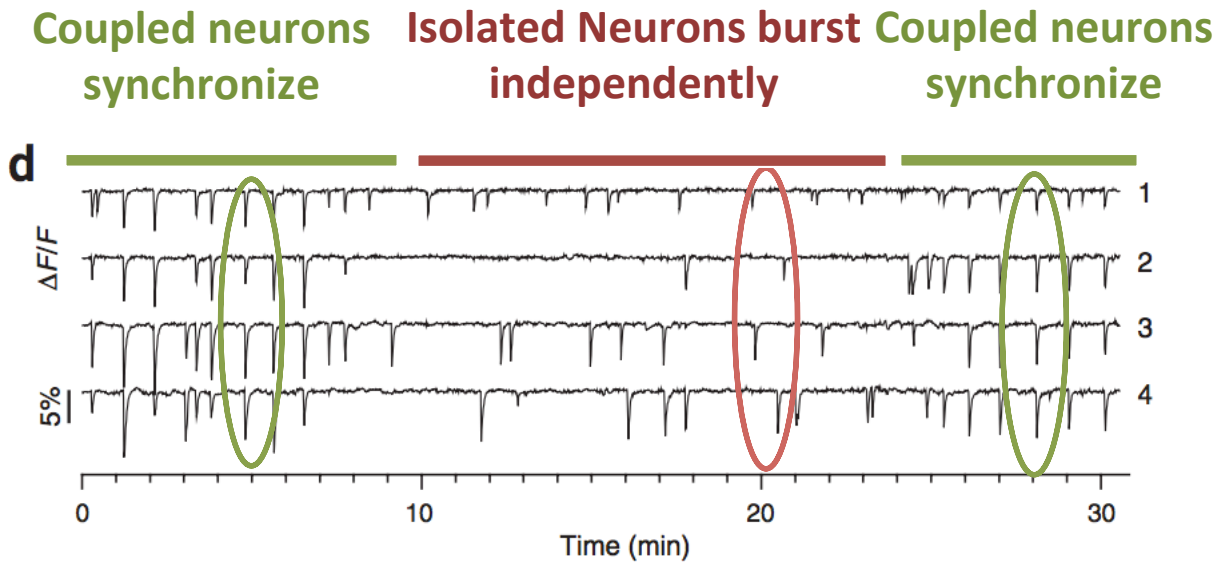


Experiment for coupled and isolated neurons, Zheng et al., 2006, Nature

Why study retinal waves?

Strategy:

To propose a model (i) sufficiently close from biophysics to explain and propose experiments and (ii) sufficiently well posed mathematically to analyse its dynamics upon varying biophysical parameters (development - pharmacology).

- Modelling one cell bursting
- Modeling cells coupling
- Modelling waves generation, propagation and termination.

Why study retinal waves?

Strategy:

To p ***and propose*** ***analyse its*** ***t -***

Multiscale modelling

From ionic channel to neuron to retina scale

Non linear dynamics, dynamical systems theory, statistical physics.

- Mod
- Modeling cells coupling
- Modelling waves generation, propagation and termination.

Main assumption

There are a few physiological parameters controlling retinal waves dynamics, evolution and variability.

Find these parameters from a mathematical analysis

Bifurcation theory

A network model for stage II retinal waves

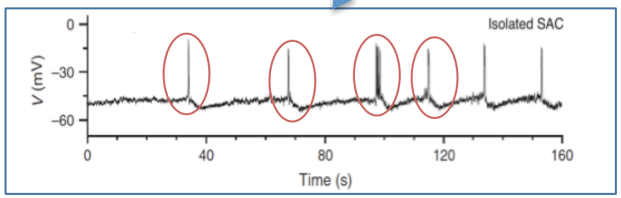
A network model for stage II retinal waves

Membrane potential dynamics

$$C_m \frac{\partial V}{\partial t} = -g_L^M (V - V_L) - g_{Ca}(V)(V - V_{Ca}) - g_K N (V - V_K)$$

$$\tau_N \frac{\partial N}{\partial t} = \Lambda(V)(N_\infty(V) - N)$$

Morris-Lecar & Fast K+ channels



A network model for stage II retinal waves

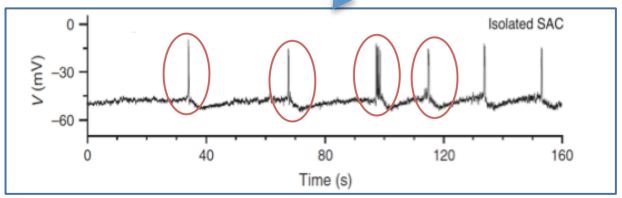
Membrane potential dynamics

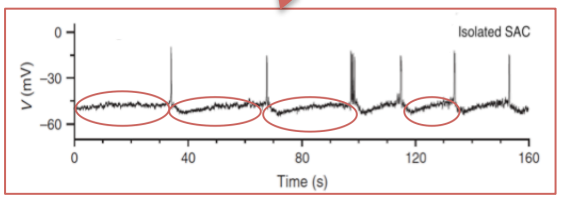
$$C_m \frac{\partial V_i}{\partial t} = -g_L^M (V_i - V_L) - g_{Ca}(V_i)(V_i - V_{Ca}) - g_K N_i (V_i - V_K) - g_{sAHP} R_i^4 (V_i - V_K)$$

$$\tau_N \frac{\partial N}{\partial t} = \Lambda(V)(N_\infty(V) - N)$$

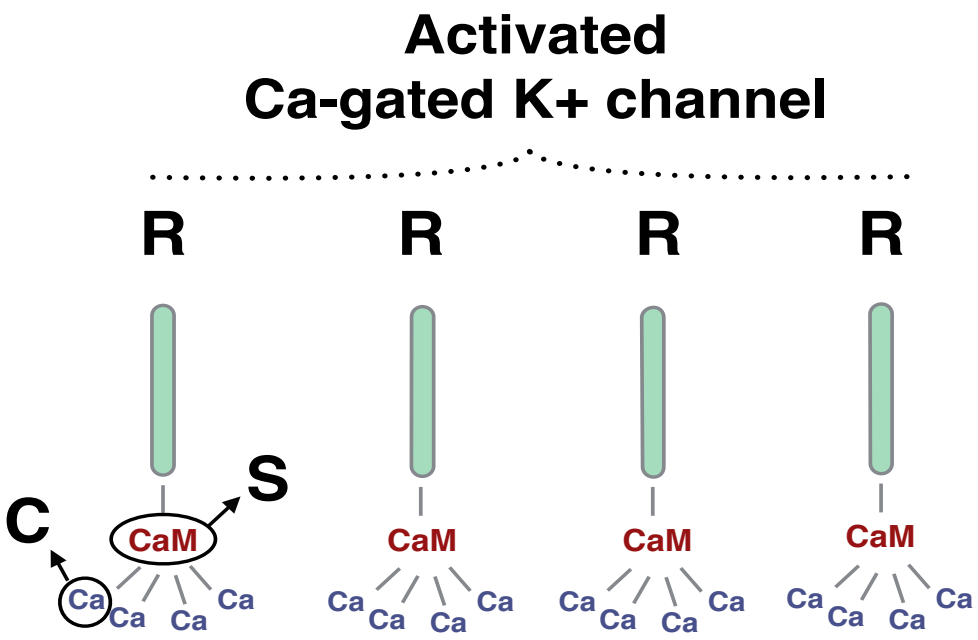
Morris-Lecar & Fast K+ channels

sAHP current Refractory mechanism





Set of equations for sAHP current



Gating mechanism

All 4 subunits R of the channel are bound to activate the channel

⇧

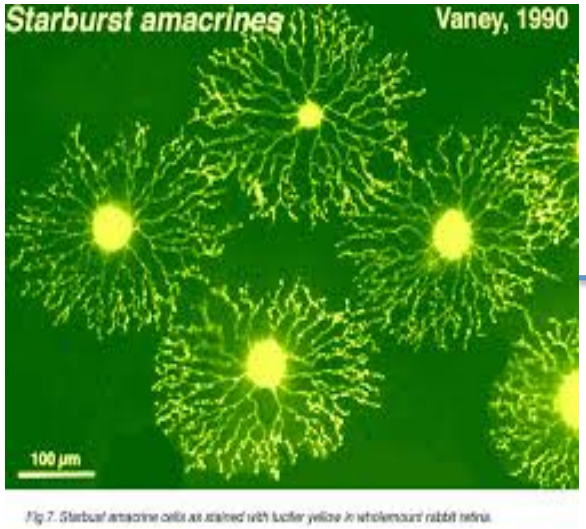
Saturated Calmodulin molecule (CaM) bind to each channel subunit

⇧

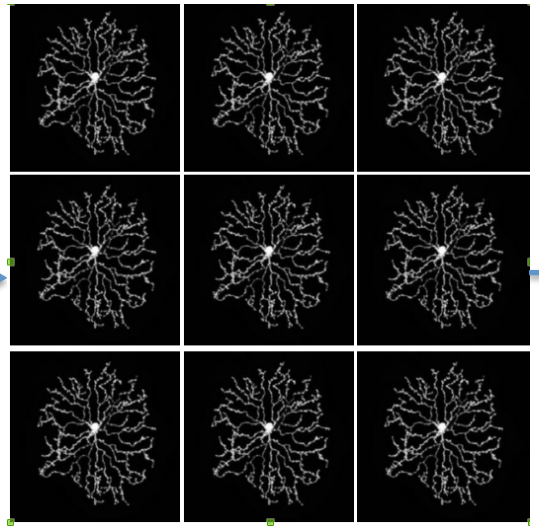
4 Calcium ions bound to each saturated Calmodulin complex S

SACs Network

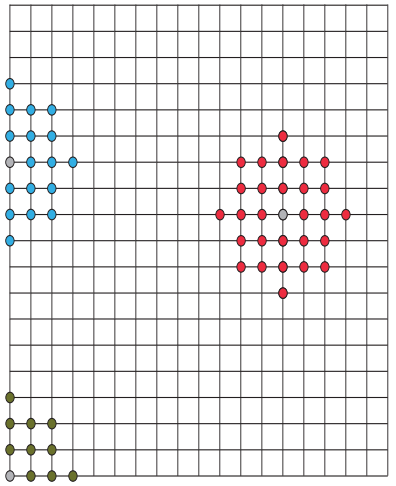
Model synaptic interactions



SACs realistic connections



SACs on a lattice



SACs become points on a lattice

A network model for stage II retinal waves

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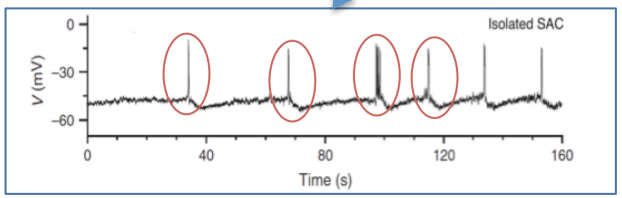
$$C_m \frac{\partial V_i}{\partial t} = -g_L^M (V_i - V_L) - g_{Ca}(V_i)(V_i - V_{Ca}) - g_K N_i (V_i - V_K) - g_{sAHP} R_i^4 (V_i - V_K) - \sum_j g_{j,Ach}(A_j)(V_i - V_{Ach})$$

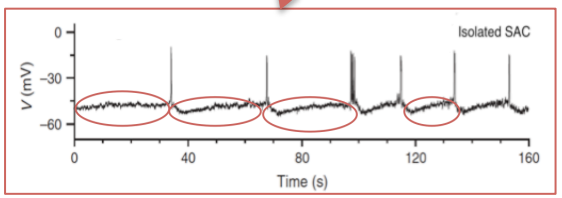
$$\tau_N \frac{\partial N}{\partial t} = \Lambda(V)(N_\infty(V) - N)$$

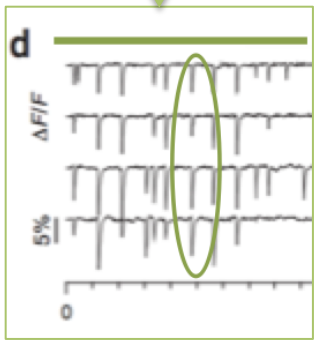
Morris-Lecar & Fast K+ channels

sAHP current
Refractory mechanism

Ach current
Network effect







Spontaneous Bursting Mechanism of SACs

Bursting
sAHP

1. Bursting

V
Voltage -70 mV
60mV
N
K+ gating
0
0.8
20 s

Increase of Calcium load during bursting

2. Calcium Buffering

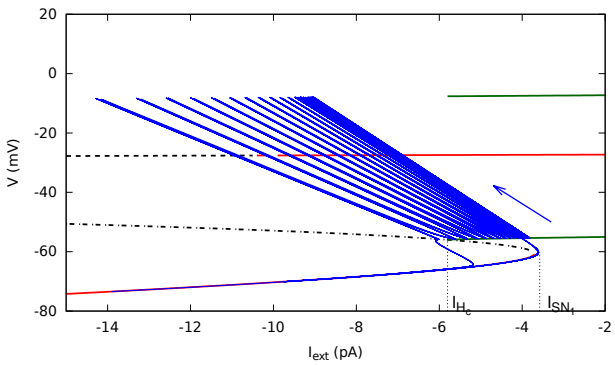
C
Intracellular Calcium Concentration
88 nM
300 nM
20 s

Calcium controls the sAHP phase. Voltage is low and Calcium starts offloading

3. sAHP

R
Ca-dependent K+ gating
0.4
0.2
S
Probability of Calmodulin binding
0.2
0.4
20 s

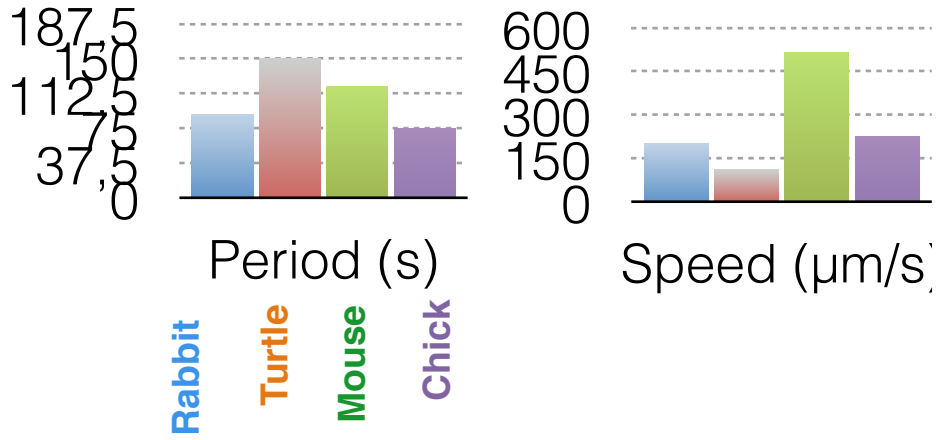
Bursting starts again when the Calcium load is low enough



Variability within retinal waves

i) Across species

Godfrey et al. 2007



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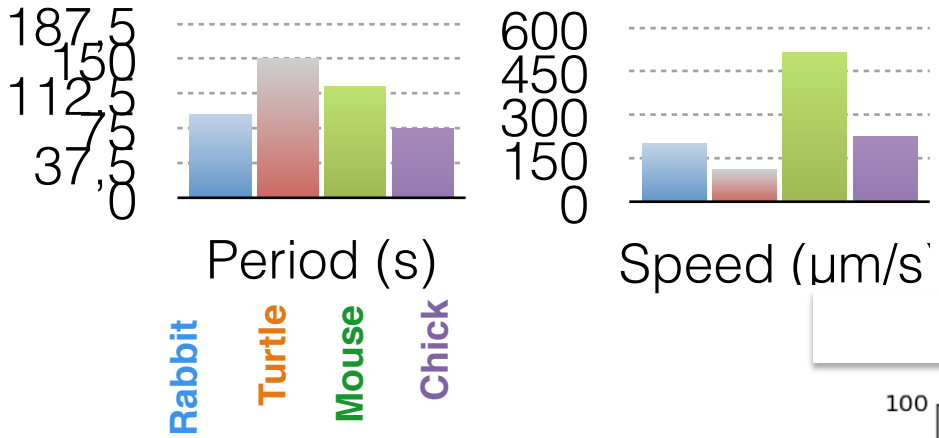
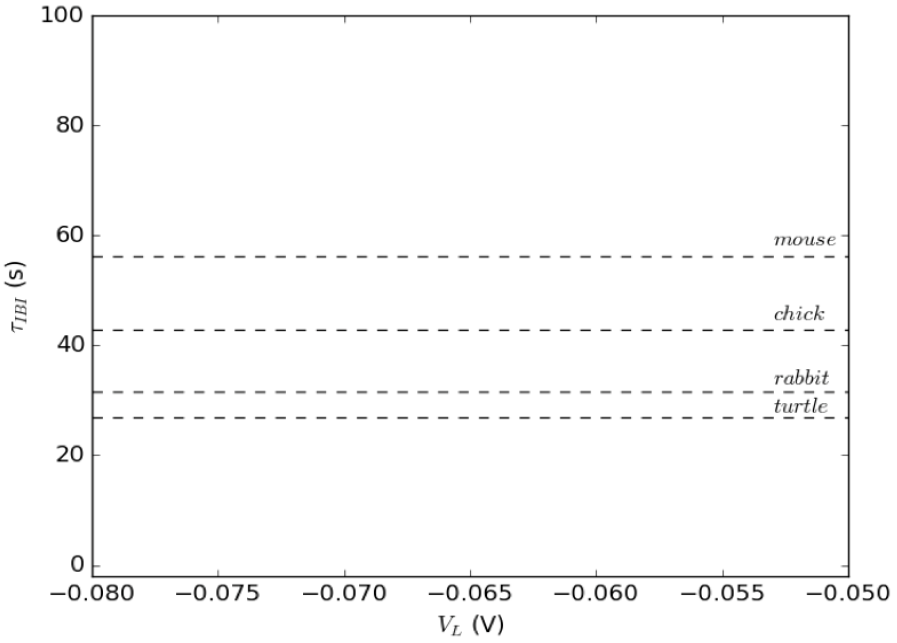


Interburst intervals



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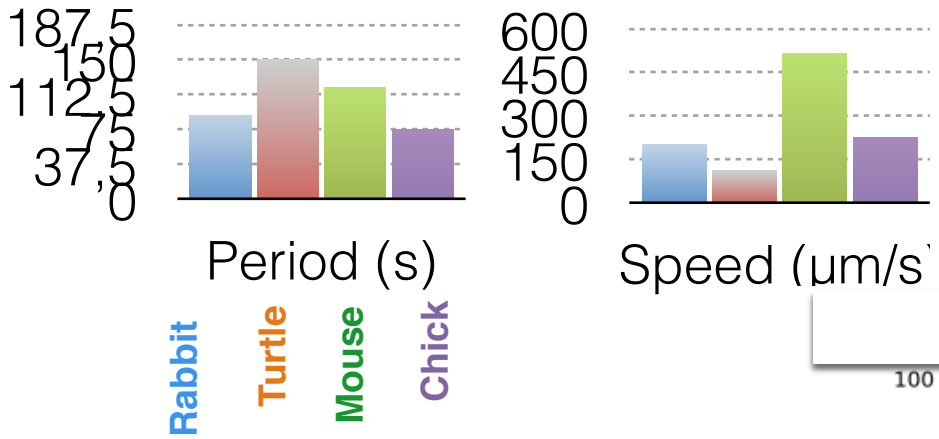

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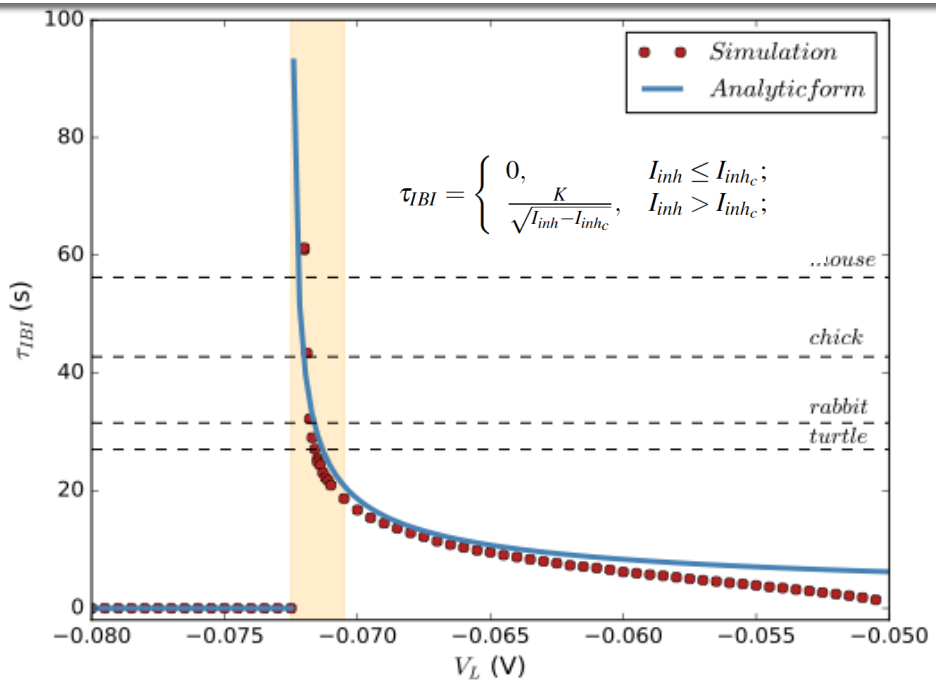
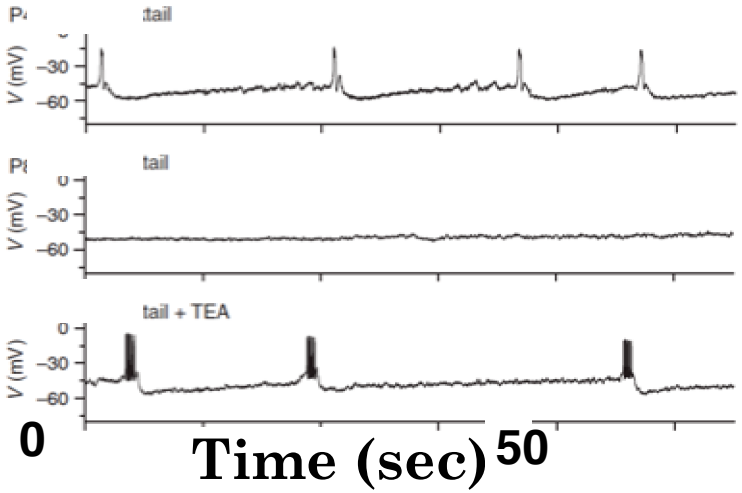


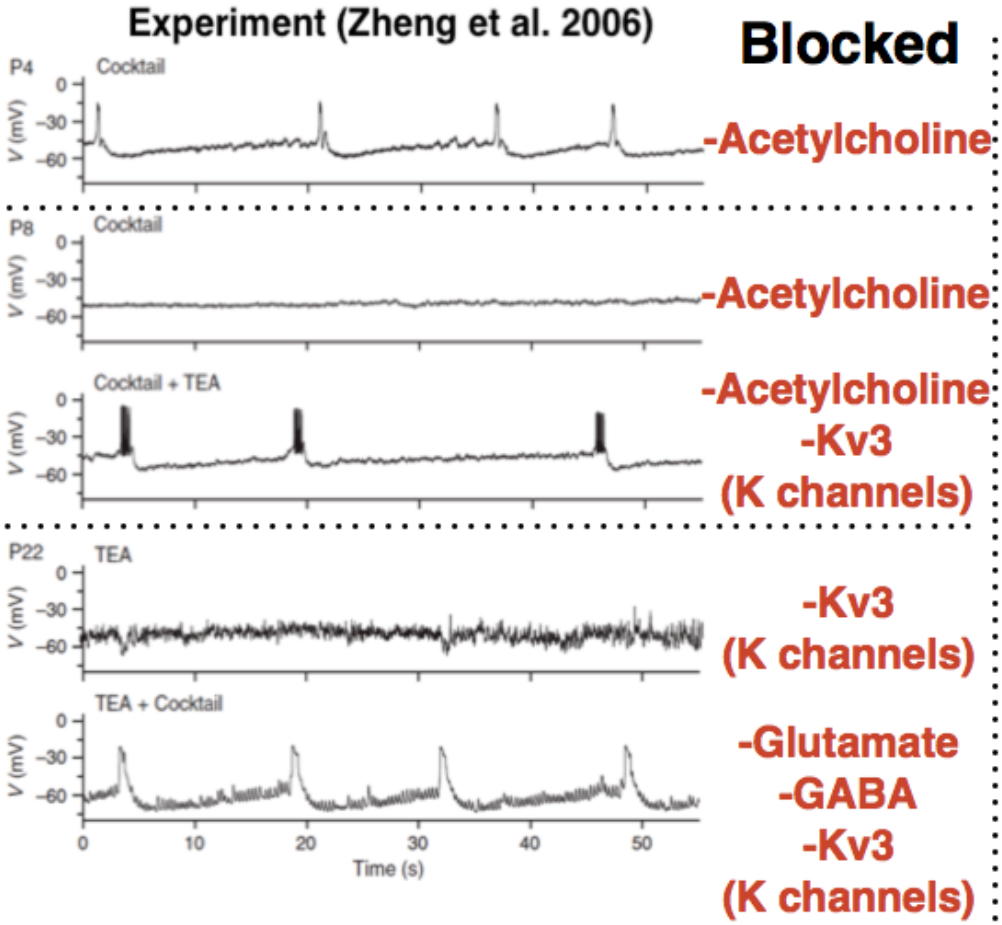
Variability within retinal waves

iii) Pharmacology



How do SACs lose their excitability?

A



Potassium channels (potentially Kv3) are modelled by 3 parameters

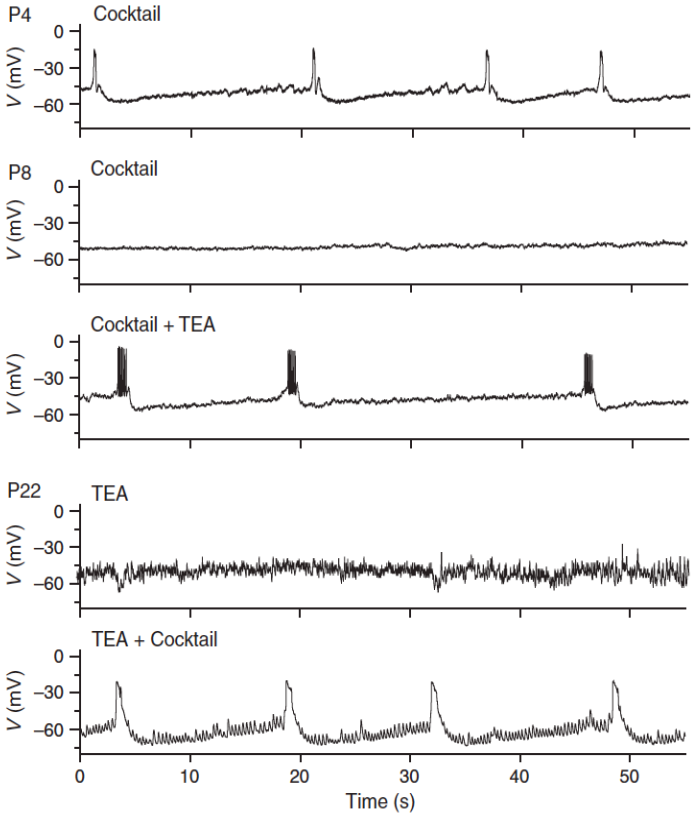
gK, V3, V4

*TEA blocks Kv3 channels

Predict the role of Kv3 channels in the loss of SACs excitability

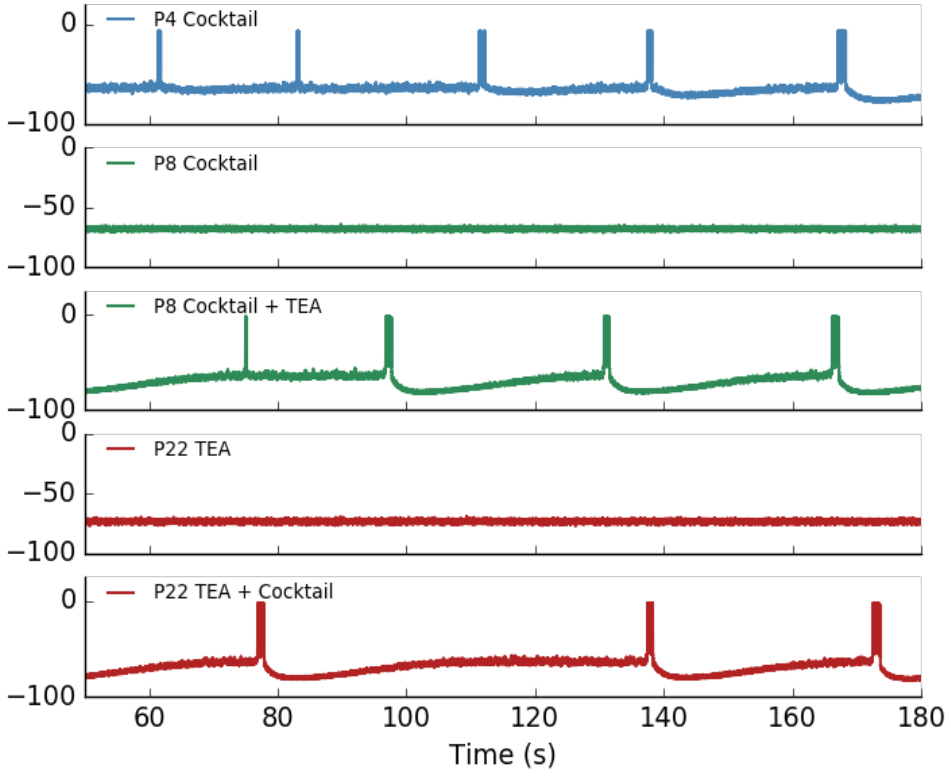
A

Experiment (Zheng et al. 2006)



B

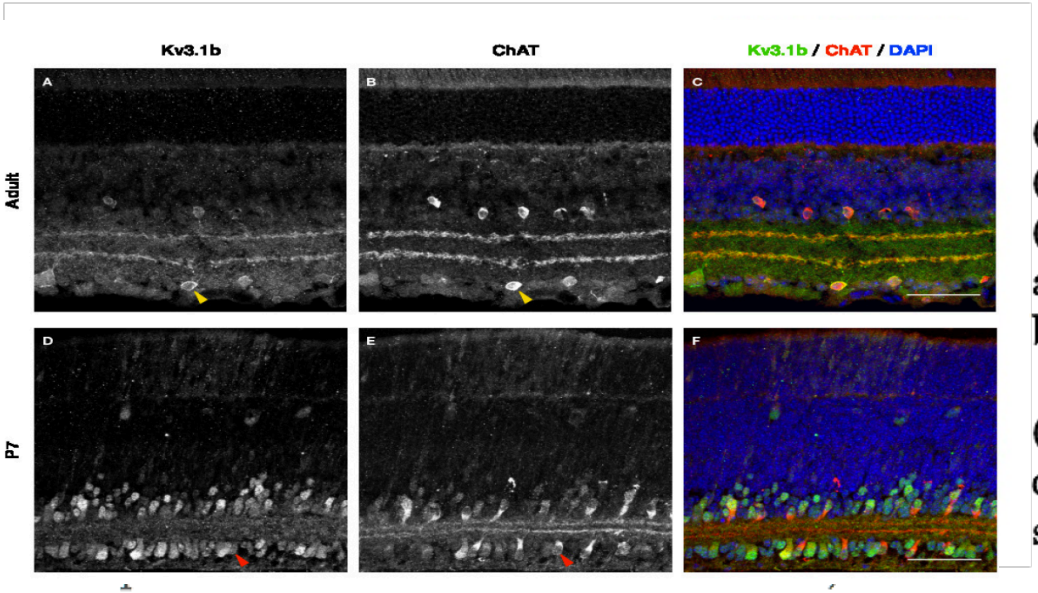
Model



How do SACs lose their excitability?

Hypothesis: The expression of the potassium Kv3 channels increases upon maturation possibly leading to the loss of SACs excitability

Preliminary experimental exploration



(O.Marre-E. Orendorff)

Localization of Kv3.1b in adult and P7 retinas.

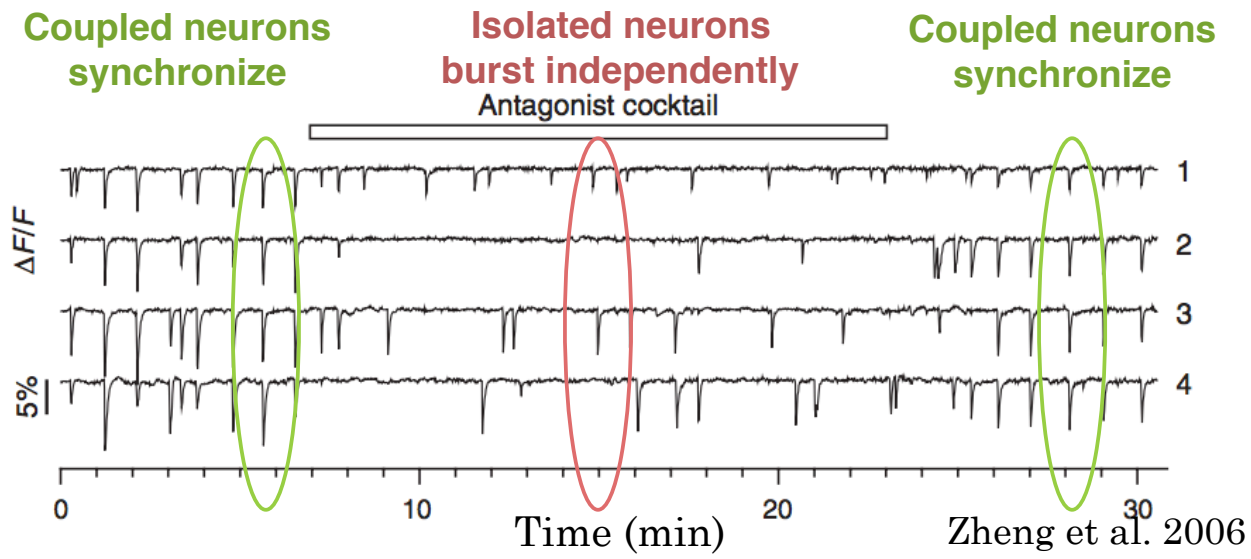
(A-C) Adult retina section showing Kv3.1b (green) and choline acetyltransferase (ChAT, red) reactivity in starburst amacrine cells. Cell nuclei stain (DAPI, blue).

(D-F) P7 retina section showing little colocalization of Kv3.1b with ChAT in starburst amacrine cells.

However, results are preliminary as experiment is not yet conclusive

Cellular mechanisms of stage II retinal waves

C. Synchrony through Acetylcholine



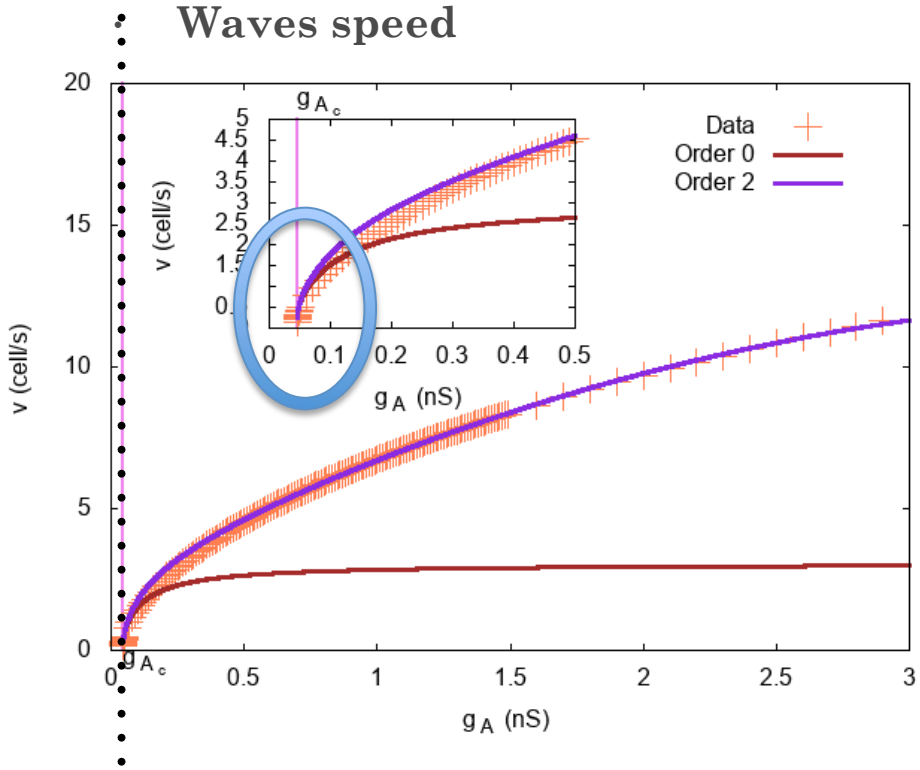
Zheng et al. 2006

Mutual excitatory connections between SACs through Acetylcholine

X

Waves speed

$$v_0 = \frac{1}{t_C - \frac{1}{\mu}\log\left(1 + \frac{1}{g_A}\frac{2\mu\sqrt{\gamma_A}}{d\beta\Omega}\left(\frac{I_{SN}+g_{sAHP}R^4(V_- - V_K)}{(V_- - V_A)}\right)\right)}$$

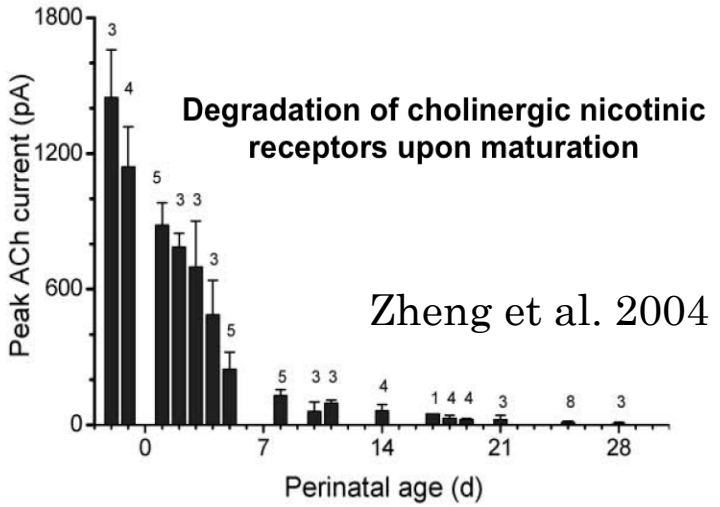


Propagation threshold

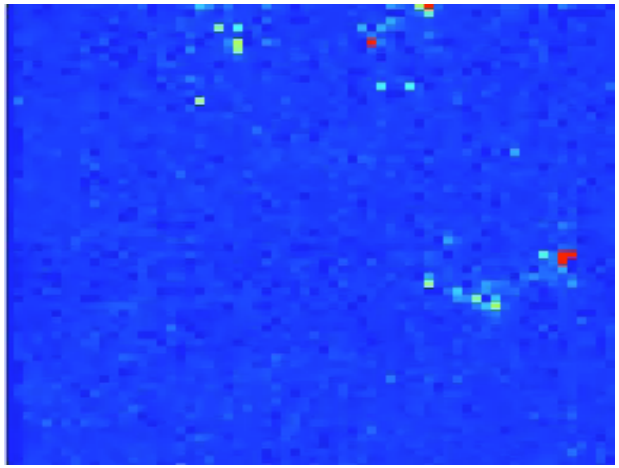
$$g_{A_c} = -\frac{2\,\mu\sqrt{\gamma_A}}{n_i\beta\Omega}\,\frac{I_{SN} + g_S R^4(V_- - V_K)}{V_- - V_A}$$

Variability within retinal waves

ii) Development

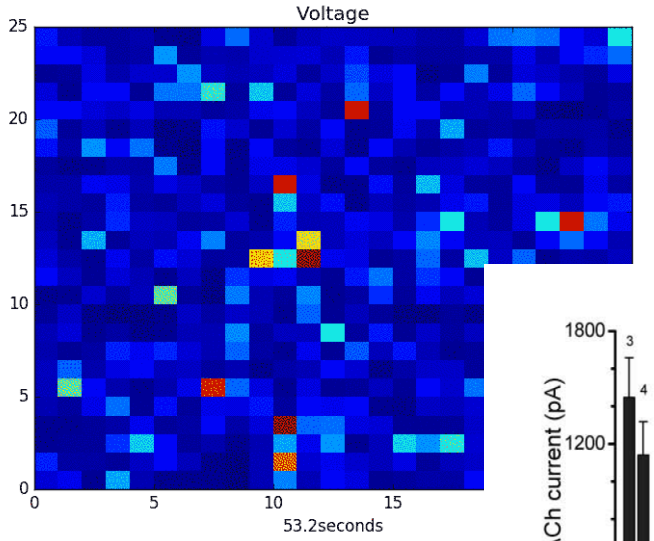


iv) Spatial Variability

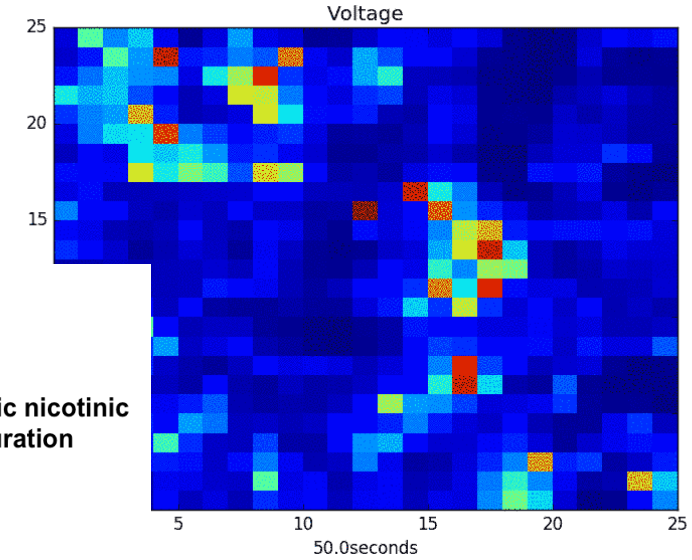


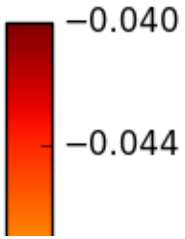
Network of SACs : Simulated Voltage

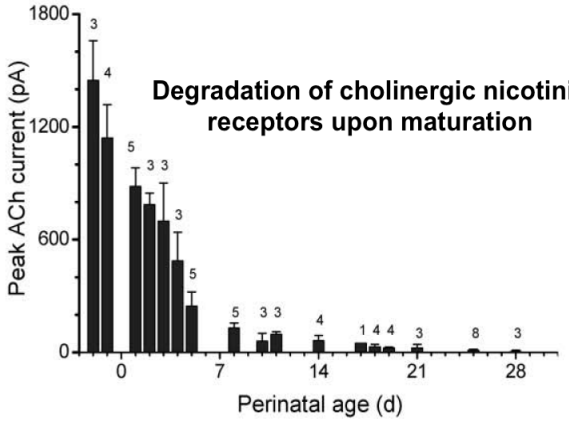
Isolated Neurons



gach=0.126 nS







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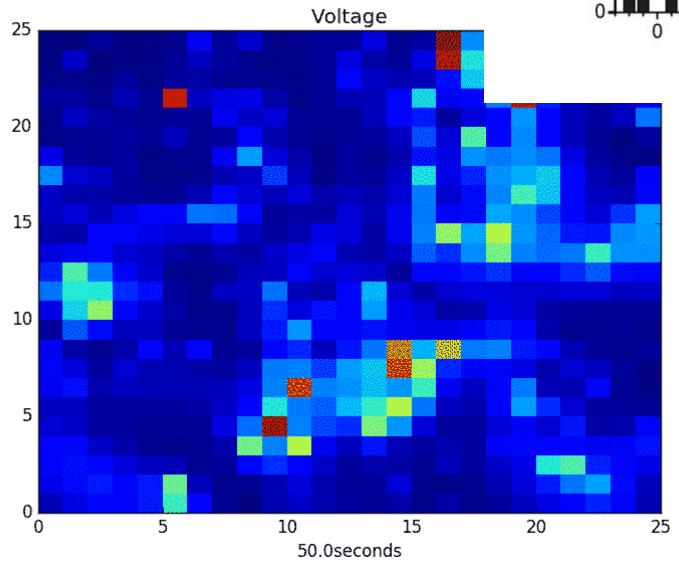
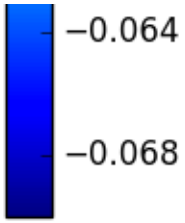
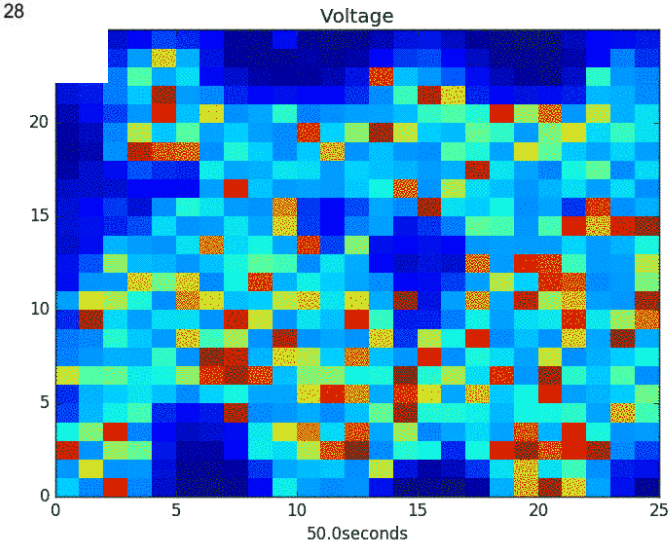


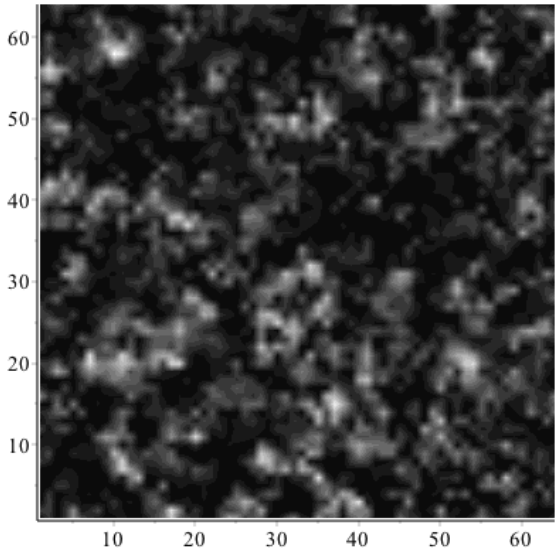


gach=0.21 nS

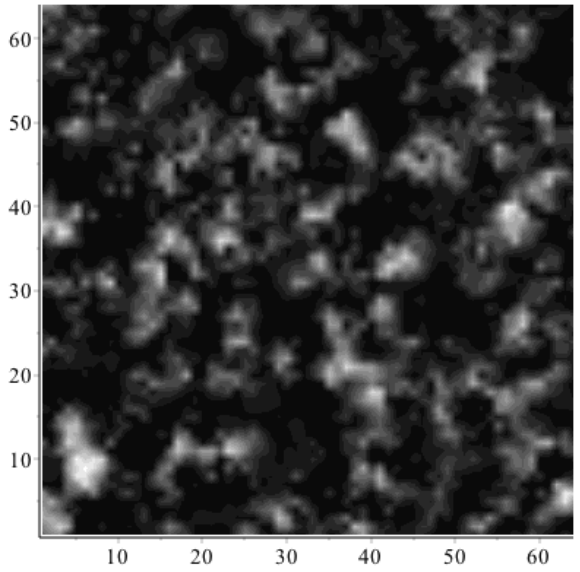


Network of SACs : Simulated Calcium Concentration

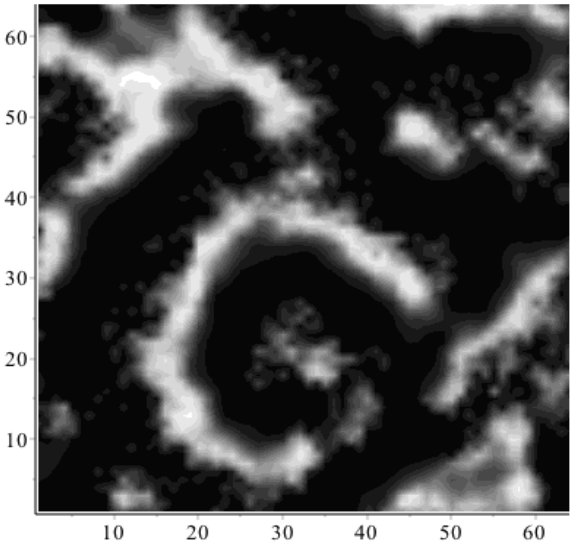
gach=0.102 nS



gach=0.126 nS



gach=0.168 nS



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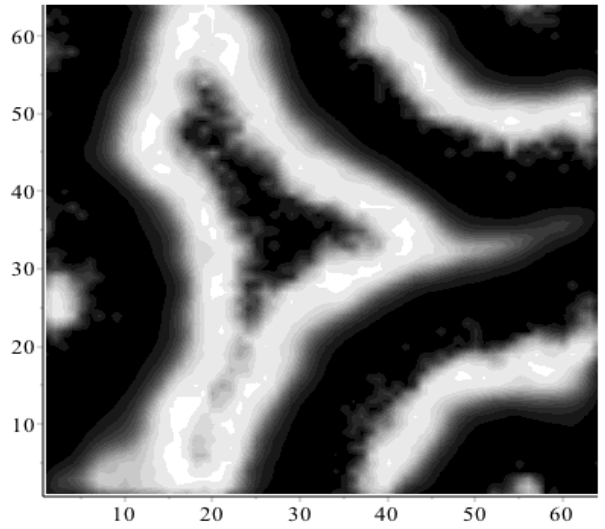
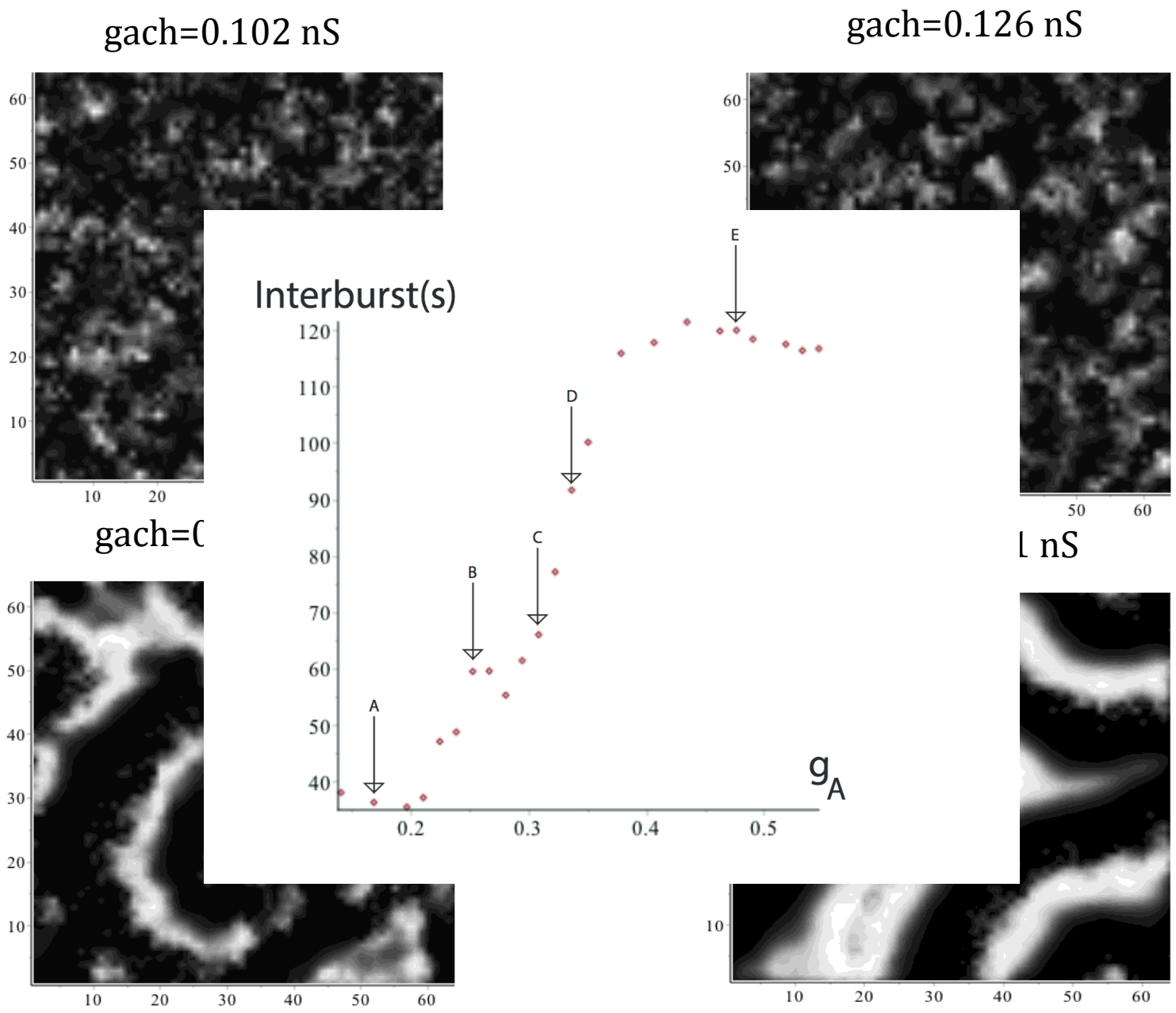


Network of SACs : Simulated Calcium Concentration

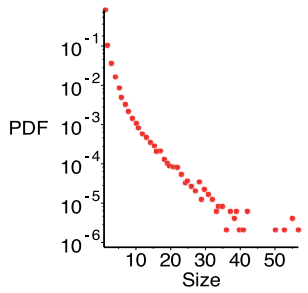


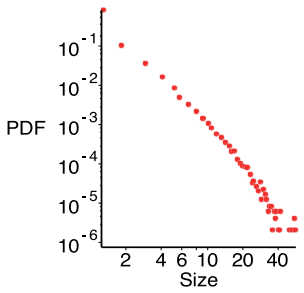
Waves size distribution

lin-log

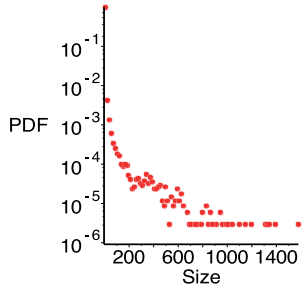
log-log

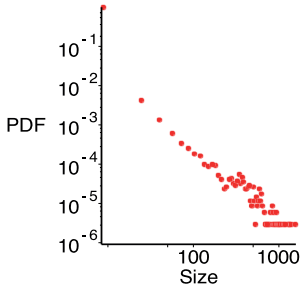
A



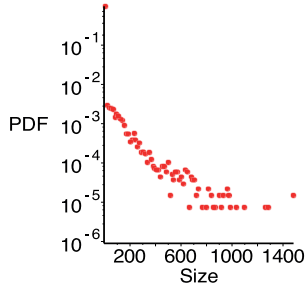


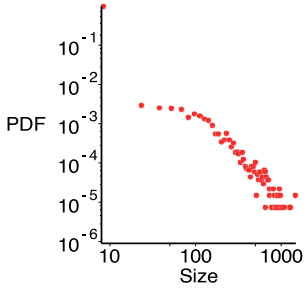
B



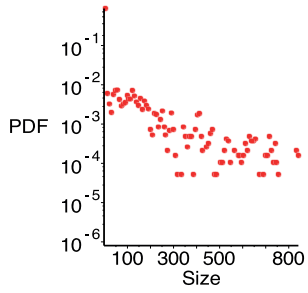


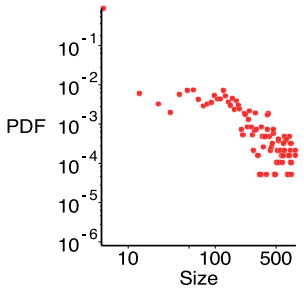
C

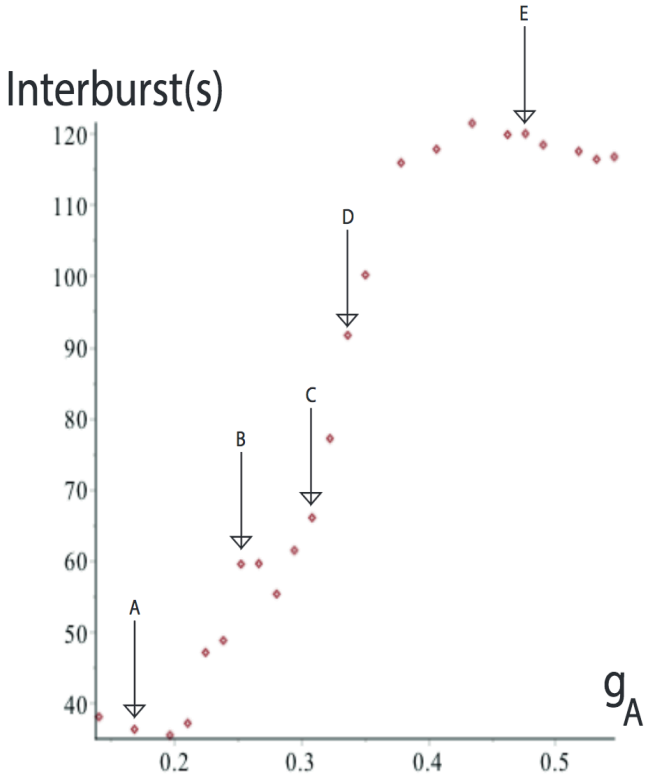




E





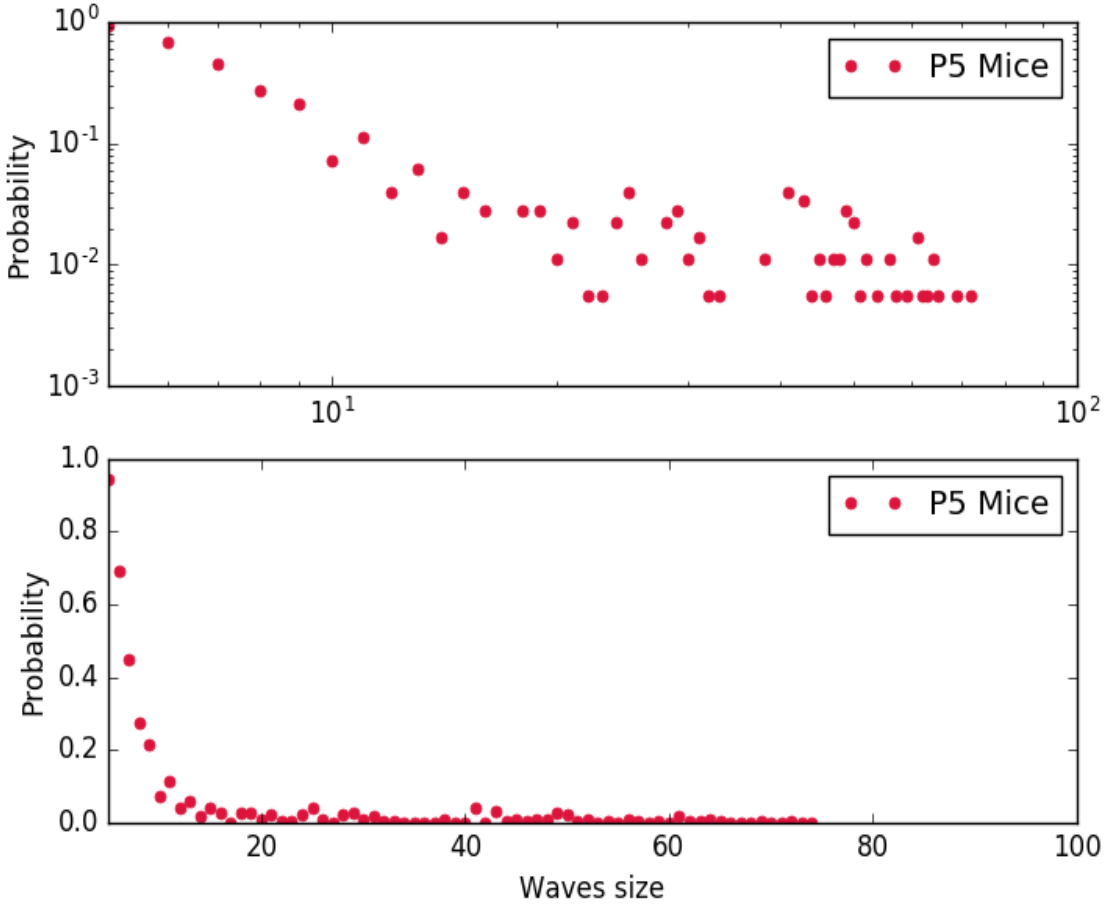


N-neuron model

- There is a **competition** between 2 mechanisms:
  - Period variability which tends to desynchronise
  - Acetylcholine which tends to synchronise
- There is an intermediate regime of coupling, where **variability** is maximum
- Therefore there is a wide repertoire of patterns
  - **Weak coupling** leads to small **localised activity**
  - **Moderate coupling** leads to **propagating patterns**
  - **Strong coupling** leads to **complete synchrony** of neurons

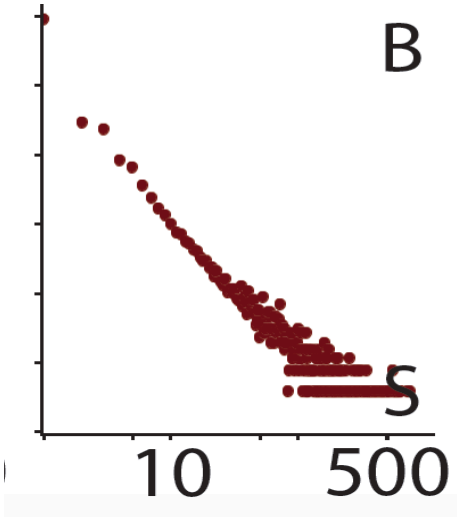
Experimentally varying Ach conductance (Data D. Karvouniari + Institut de la Vision)

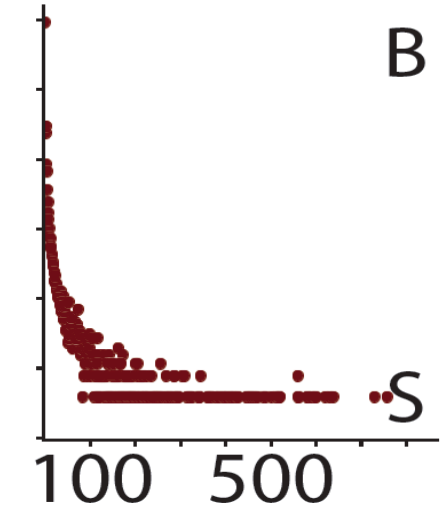
Experiment



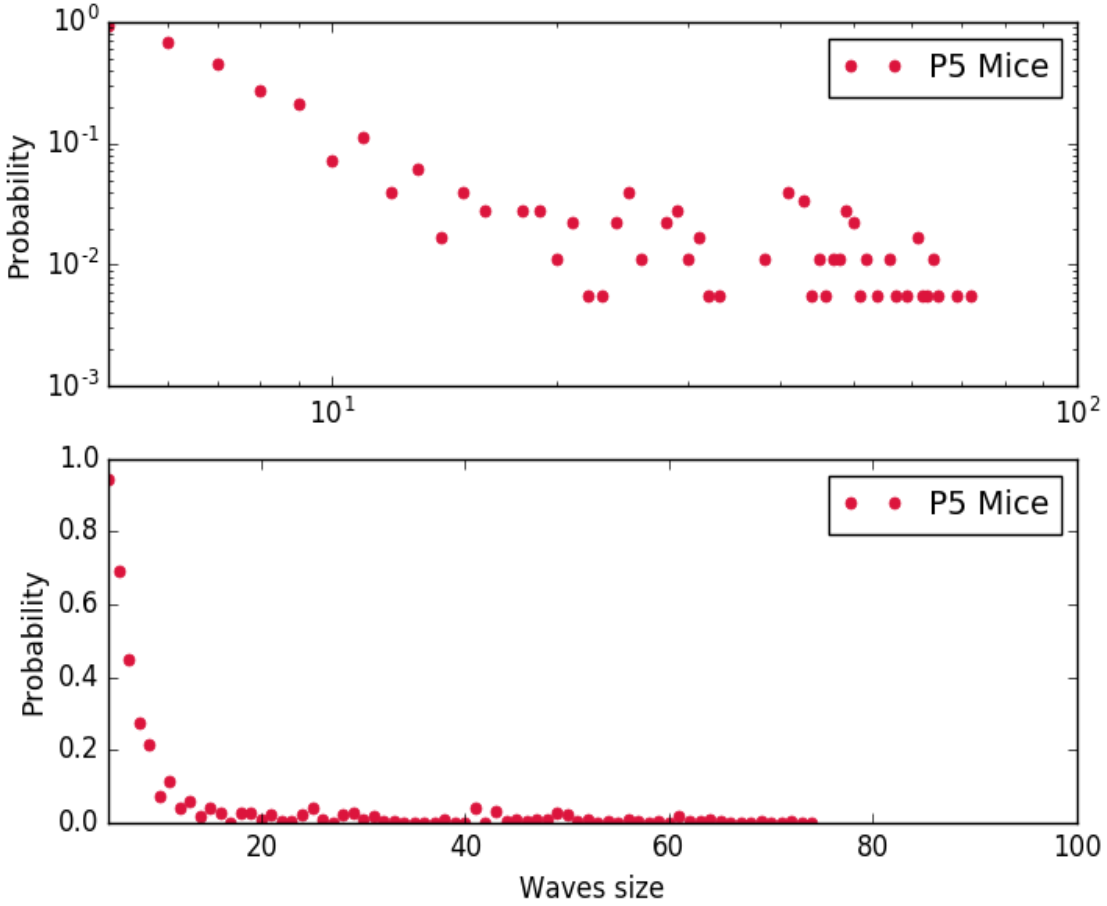
Experimentally varying Ach conductance (Data D. Karvouniari + Institut de la Vision)

Model





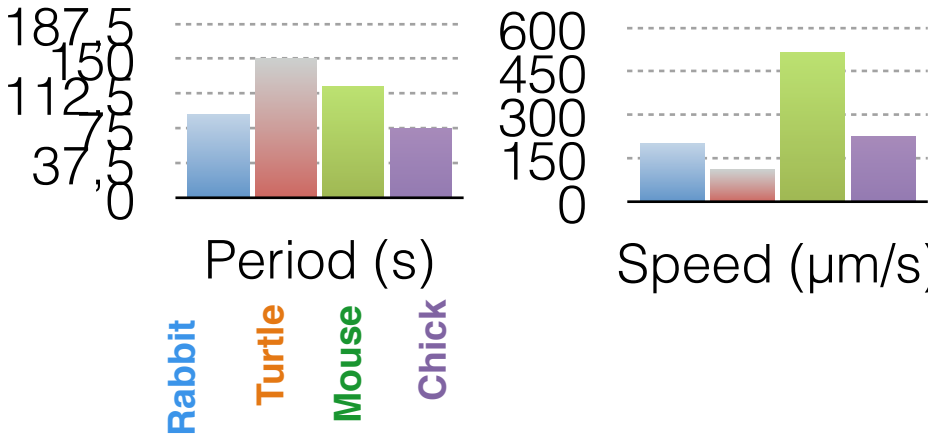
Experiment



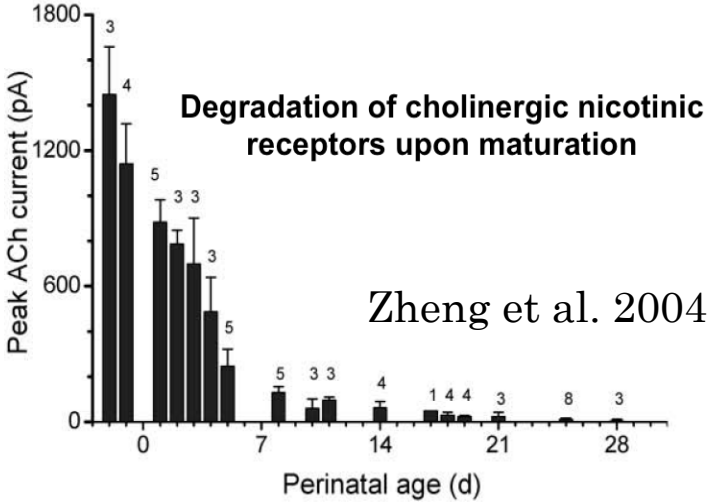
Variability within retinal waves

i) Across species

Godfrey et al. 2007

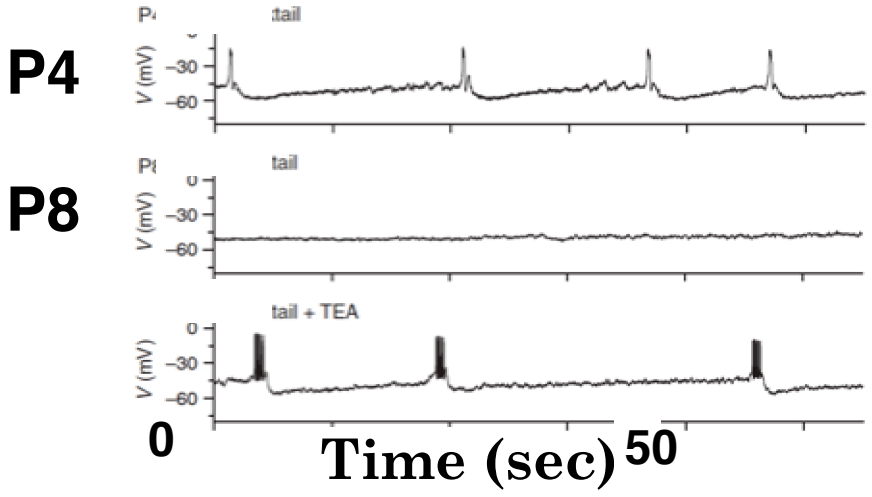


ii) Development

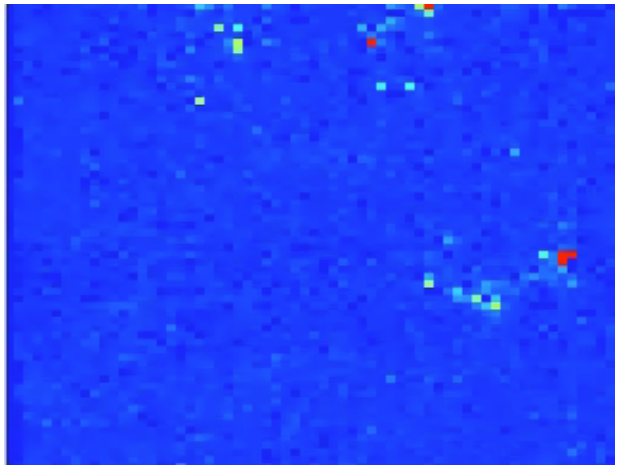


Zheng et al. 2004

iii) Pharmacology



iv) Spatial Variability



Conclusion

- **Biophysical model of stage II retinal waves relevant at:**
  - The cells scale (bursting, experimental match and predictions)
  - The network scale (waves propagation)
  - The developmental level (evolution of ionic channels and synapses).

- **Theoretical description via bifurcation theory**
  - Bursting
  - Interburst variability
  - Waves patterns

- **Next step: reactivating waves in adults.**